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# Positive modulators of the α7 nicotinic receptor against neuroinflammation and cognitive impairment in Alzheimer's disease

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ABSTRACT

Evidence so far indicates that therapies targeting a single aspect of Alzheimer's disease (AD) have no sufficient efficacy in diminishing long-term the progression of AD. Neuroinflammation is an early event during the development of the disease and it is thought to exacerbate the abnormal aggregation of the amyloid beta peptide (Aβ) and the microtubule associated protein Tau. Inhibition of gliosis is considered fundamental to reduce neuroinflammation, oxidative stress, apoptosis and synaptic dysfunction driving the progression of AD. Drugs that are able to target more than one aspect of the pathology may have higher chances of success. Modulators of α7 nicotinic acetylcholine receptors (α7nAChRs) such as nicotine and some of its derivatives have this potential because of their anti-inflammatory, anti-apoptotic, pro-cognitive and anti-protein aggregation effects. However, the rapid desensitization of α7nAChRs is considered an important factor limiting its potential therapeutic use. In here, in light of current evidence, the objective of this review is to discuss the advantages and potential therapeutic value of positive allosteric modulators (PAMs) of the nAChRs in halting or delaying the progression of AD by diminishing neuroinflammation, abnormal protein aggregation and synaptic dysfunction.

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**Contents**



*Abbreviations:* Aβ, amyloid β; AD, Alzheimer's disease; Akt, protein kinase B; ANOVA, analysis of variance; APP, amyloid beta precursor protein; BDNF, Brain-derived neurothrophic factor; FAD, familial Alzheimer's disease; GSK3β, glycogen synthase kinase 3β; nAChRs, nicotinic acetylcholine receptors; NFT, neurofibrillary tangles; NMDA, N-methyl-D-aspartate; NT, non-transgenic; PHF, paired helical filaments; PS1, presenilin 1; RAWM, radial arm water maze, Serserine, PNU-120596 1-(5-chloro-2,4-dimethoxy-phenyl)-3-(5-methyl-isoxazol-3-yl)-urea; PNU-282987, N-[(3R)-1-azabicyclo [2.2.2] oct-3-yl]-4-chlorobenzamide; SB-206553, 3,5-dihydro-5-methyl-N-3-pyridinylbenzo [1,2-b:4,5-b′]-di pyrrole-1(2H)-carboxamide; PSD95, Postsynaptic density protein 95; Tg, transgenic; TNF, tumor necrosis factor.

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## 1. Role of neuroinflammation in Alzheimer's disease

Alzheimer disease (AD) is the main cause of dementia with approximately 27 million people affected worldwide. The Alzheimer's association recently reported that every 67 s a new person is diagnosed with AD only in the USA (Association, 2015). AD progresses insidiously from a mild cognitive impairment (MCI) to a total suppression of a person's ability to carry out the more simple daily activities. AD reduces synaptic plasticity in regions of the brain that are mainly involved in high level cognitive functions such as the hippocampus, and the prefrontal cortex. The major neuropathological hallmarks of AD are the presence of extracellular Aβ plaques, intracellular neurofibrillary tangles (NFT) of the microtubule associated protein Tau and neuroinflammation (Wyss-Coray and Rogers, 2012). New advances in the diagnosis of the pathology offers new opportunities of early treatment (Perrin et al., 2009). Neuroinflammation seems to be an important contributory factor in the development of AD and occurs early during the pathology (Parachikova et al., 2007; Xu et al., 2014). Neuroinflammation involves an innate immune reaction resulting in a self-attack on neuronal cells. This phenomenon named autotoxicity differs from autoimmunity which involves cloning of peripheral lymphocytes (McGeer and McGeer, 2000). The progression of AD is always accompanied by an abnormal activation of many inflammatory pathways (Najem et al., 2014; Streit et al., 2014) (Fig. 1).

### 1.1. Role of autotoxicity in Alzheimer's disease

New evidence gathered throughout the International Genomics of Alzheimer's Project (IGAP) strongly supports the view that an alteration of the immune response is central in the developing of late-onset AD. This project investigated genetic causes of late-onset

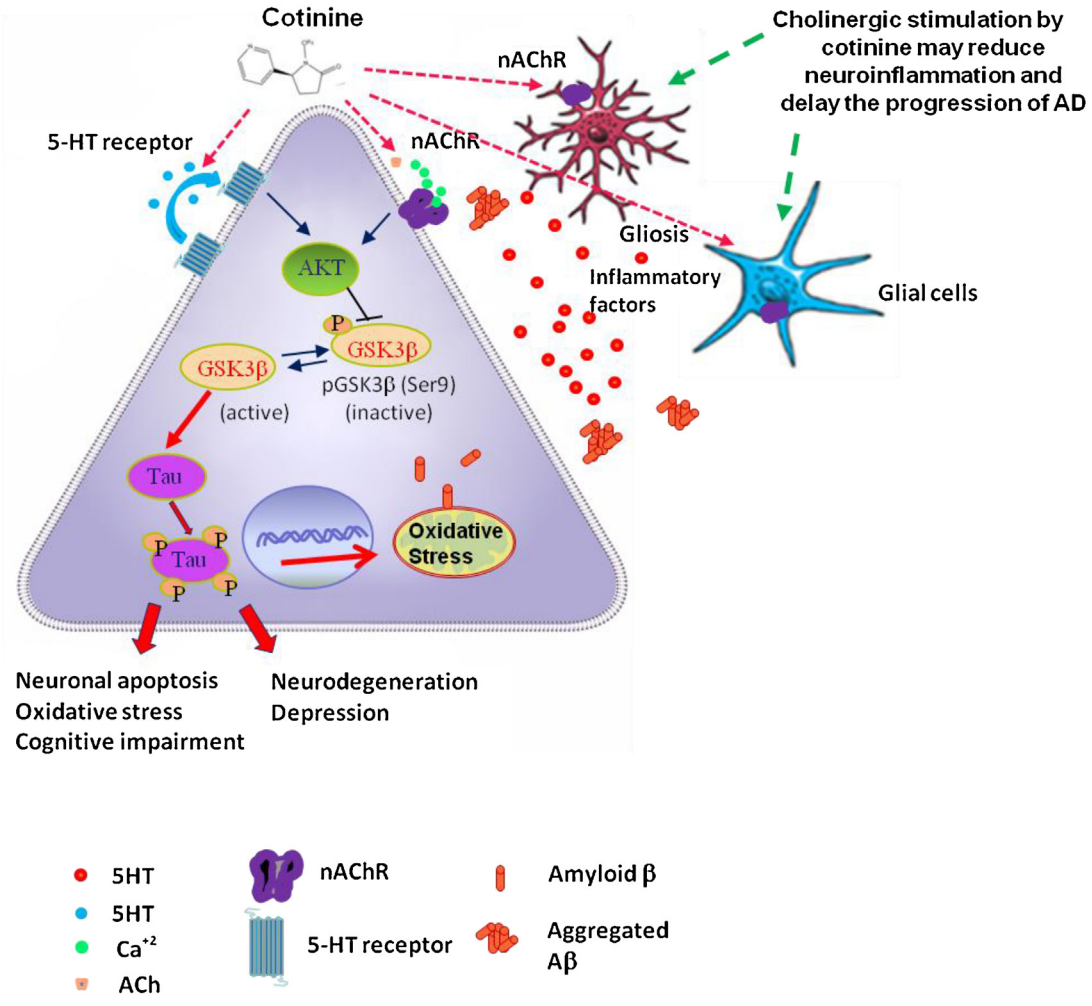


**Fig. 1.** *Positive allosteric modulation of α7 nicotinic acetylcholine receptors can decrease Alzheimer's disease neuropathology.* Diagrammatic view of the effect of cotinine in decreasing oxidative stress, Aβformation, tau hyperphosphorylation and neurodegeneration by stimulating the α7nAChRs and facilitating serotonin (5-HT) release. The molecular mechanism would involve the activation of the protein kinase Akt and the inhibition by phosphorylation of GSK3β.

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AD; the data obtained revealed that late-onset AD was genetically linked to 20 genes showing genome-wide association. Analysis of the IGAP data was performed using the ALIGATOR and GSEA algorithms to identify associated functional pathways and to correlate them to changes in gene expression in the human brain. ALIGATOR identified several biological pathways showing enrichment of association. The immune response, endocytosis, cholesterol transport and protein ubiquitination represented the main pathways associated to the development of AD. From these pathways, the immune response pathways represent exceptional targets for AD therapeutics. Many inflammatory factors have been identified in AD brains showing accumulation of aggregated forms of the Aβ (McGeer and McGeer, 2001, 2002). The accumulation of Aβpeptides, which are derived from the proteolysis of the transmembrane protein named Aβ precursor protein (APP), is accompanied by increased levels of several inflammatory factors in the brain including the pentraxins C-reactive protein; complement proteins; inflammatory cytokines interleukin-1 (IL-1), IL-6 and tumor necrosis factor-alpha (TNF-α); the protease inhibitors alpha-2-macroglobulin and alpha-1-antichymotrypsin; and the prostaglandin generating cyclooxygenases COX-1 and COX-2 (McGeer and McGeer, 2001, 2002). These factors are thought to be involved in the progression of the pathology.

Several lines of evidence, obtained in mouse models of AD, suggest that neuroinflammation can contribute to exacerbate Tau pathology in AD. In one of these studies, it was shown that blocking IL-1 signaling using an antibody against its receptor greatly attenuated Tau-pathology in the triple transgenic AD mice (3xTg-AD) expressing a mutant form of Tau (Kitazawa et al., 2011). They showed that this inhibition reduced the cerebral activity of several tau kinases, including glycogen synthase kinase-3 (GSK-3), cyclin-dependent kinase (cdk5), p38-mitogen-activated protein kinase (MAPK), and the neuronal Wnt/β-catenin pathway while reducing the level of phosphorylated Tau in the brain. This evidence permitted to connect the increase in IL-1β and neuroinflammation with the activation of GSK-3β and Tau phosphorylation (Ghosh et al., 2013).

It has been hypothesized that differences in gender-linked susceptibility to AD can be related to the inflammatory processes. Indeed, it is estimated that for a 65-year-old woman the lifetime risk of developing AD, doubles the risk for a man of the same age. According to the American Autoimmune Related Diseases Association, women have a higher prevalence of autoimmune disorders (www.aarda.org). Based on these epidemiological data it has been suggested that the higher susceptibility of women to develop autoimmune conditions, predispose them to have AD, a condition that also involves autotoxic mechanisms (McGeer and McGeer, 2011). Age-related diseases, that are associated with the disruption of the blood–brain barrier (BBB) such as AD, have in common a deterioration of cognitive abilities that progresses to dementia. The abnormal presence of immunoglobulins (Igs) in the brain parenchyma and degenerating neurons having vascular-derived antibodies and complement components, suggests an autoimmune or autotoxic component in AD. It has been speculated that auto-antibodies in the serum able to react with neurons have no pathological consequences until there is a dysfunction of the BBB allowing them to access their targets and produce neurodegenerative effects in the brain. This evidence, suggests the occurrence of autoimmunity-induced neuronal cell death in AD (D'Andrea, 2005; McGeer and McGeer, 2001).

### 1.2. Dual effect of neuroinflammation in Alzheimer's disease progression

When taking into consideration inhibiting neuroinflammation for treating AD, it is important to consider that neuroinflammation seems to have a double sword effect in AD. Abundant amount of evidence has shown that neuroinflammatory factors can elicit opposite outcomes on neuronal survival in the brain. This concept is well represented by the differential effects of prostaglandin $E_2$ ($PGE_2$) when acting on different PG receptors. $PGE_2$ is a key player during brain inflammation and exerts its neuromodulatory actions by activating four G-protein-coupled receptors, $EP_1$, $EP_2$, $EP_3$, and $EP_4$. A previous study using primary neuronal cultures showed that neurons express the four $EP_{1-4}$ receptors and that neuronal stimulation with low concentrations of $PGE_2$, the $EP_2$ agonist butaprost, $EP_3$/$EP_4$ receptor agonist hydroxy-$PGE_1$, but not the $EP_3$/$EP_1$ agonist sulprostone were neuroprotective (Echeverria et al., 2005). The neuroprotective activity of the $EP_2$/$EP_4$ receptors correlated with a significant increase of intra-neuronal cyclic adenosine monophosphate (cAMP) level (Echeverria et al., 2005). Activation of the protein kinase A (PKA) by cAMP mediated the protective effects of the $EP_2$ receptor as its inhibitor and analogue RpcAMPS significantly attenuated butaprost-induced neuroprotective effects. This attenuation was not observed when neurons were co-treated with RpcAMPS and 1-hydroxy-$PGE_1$ revealing different neuroprotective mechanisms triggered by $EP_2$ and $EP_4$ receptors (Echeverria et al., 2005). Furthermore, the stimulation of these EP receptors also inhibited the oxidative stress induced by Aβ exposure *in vitro* (Echeverria et al., 2005). Similar neuroprotective effect of the stimulation of EP2 receptors against 6-hydroxydopamine (6-OHDA)-induced oxidative stress and toxicity in primary rat neuronal cultures has been reported (Carrasco et al., 2008). A posterior report showed similar neuroprotective effects induced by the stimulation of $EP_2$ receptors using butaprost in a report investigating the role of $EP_2$ receptors animal and cellular models of NMDA excitotoxicity (Ahmad et al., 2006a). In this study, mice were given an intracerebroventricular injection of butaprost followed by an infusion of NMDA in the right striatum. After 48 h, a significant reduction in NMDA-induced lesion volume was observed in groups pre-treated with butaprost (1–300 nmol/L), with maximal protection at 100 nmol/L. Also, when mouse neuronal cultures were treated with butaprost and NMDA cell viability analyzed after 24 h of treatment showed an important prevention of NMDA-induced neuronal cell death. The data showed that butaprost increased neuron survival in a dose-dependent manner by a mechanism involving the increase of intracellular cAMP levels.

In a contemporary study the same group showed that C57BL/6 mice pretreated with an intracerebroventricular injection of 1-$OHPGE_1$ before inducing transient cerebral focal ischemia, showed a significant reduction in brain injury after reperfusion (>19%). Similar results were obtained investigating NMDA excitotoxicity in primary mouse neuronal cells. Co-treatment with 1-$OHPGE_1$ was also neuroprotective. This neuroprotective effect was accompanied by a more than two-fold increase of cAMP levels and the activation the extracellular signal-regulated kinases (ERKs) (Ahmad et al., 2006b). A fine balance of pro- and anti-inflammatory signals is required to prevent brain injury while clearing cellular debris and abnormally aggregated proteins and peptides. Since, PGs are the principal mediators of neuroinflammation in the CNS, it is reasonable to postulate that modulation of downstream effectors of PGs such as specific EP receptors can provide benefit against AD pathology (Cudaback et al., 2014; Dore, 2006). Recently has been shown that the genetic deletion of the EP3 receptor prevented the increase in the expression of inflammatory genes and lipid peroxidation, decreased the levels of Aβ peptides and reversed the decline in pre-synaptic proteins seen in the APPSwe-PS1 ΔE9 mice (Shi et al., 2012). On the other hand, since the blood brain barrier (BBB) deteriorates during aging, it has been postulated that changes in immune cells functionality as well as in BBB integrity, may create favorable conditions for the trespassing of viral

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infections to the brain. These brain intruders thus may trigger or amplify pre-existing neuroinflammatory processes. Altogether this cascade of event will result in abnormal protein modification and aggregation, neuronal cell death and an abnormal clearance of immunogenic cell debris and synaptic dysfunction (Marosova et al., 2014). Based in this idea, a general effect of systemic infections on the development of AD has been hypothesized (Dickson et al., 1993; Marosova et al., 2014).

### 1.3. Role of T lymphocytes in Alzheimer's disease

Also, this dual effect is observed at the cellular response level. ACh-synthesizing T lymphocytes provide an essential non-neural link in the anti-inflammatory pathway from vagus to spleen (Martelli et al., 2014). For example, the T cells are a type of lymphocyte or white blood cell that plays a central role in cell-mediated immunity. T cells trespass the BBB to accumulate and proliferate in the brain playing a key role in neuroinflammation. Activated T-cells express inflammatory factors such as cytokines which activate microglia and other immune cells to synthesize more inflammatory factors. Nevertheless, T cells can also be neuroprotective as CD4(+) Th2 cells secrete anti-inflammatory cytokines and promote the release of neurotrophins from glia. Under normal conditions the brain shows a low population of innate immune cells including microglia/macrophages and neutrophils. Under pathological conditions microglia/macrophages activate and migrate from the periphery to the site of neurodegenerative damage to release cytokines, chemokines, and pro-oxidant and apoptotic factors (Wyss-Coray, 2006; Wyss-Coray et al., 2001a; Wyss-Coray and Rogers, 2012). However, It has been found decreased numbers of T cells in the hippocampus and cortex of mild to moderate AD cases when compared to non-demented controls (Parachikova et al., 2007). This evidence suggests a dysfunction of the immune response in AD.

The major histocompatibility complex (MHC) class II proteins are located on the surface of antigen presenting cells (APCs) and their function is to present segments of endocytosed antigens to T cells, in doing so triggering adaptive immune responses. The overexpression of MHC class II proteins has been instrumental to investigate changes in innate immune cells including dendritic cells, B cells and monocytes/microglia in AD models. Also, the expression of these proteins in the brain of control and early AD dementia cases has been investigated (Itagaki et al., 1988; McGeer et al., 1989; Parachikova et al., 2007). Increased levels of MHC class II proteins expression (2.6 fold) have been found in the brain of AD patients presenting mild to moderate dementia when compared to control non-demented controls. A specific up-regulation of MHC class II was noted in the hippocampus in contrast to a broader inflammatory response in the pre-frontal cortex of these AD patients. MHC class II molecules have been found co-localized with reactive microglia but no astrocytes (McGeer et al., 1989). The MHC positive microglia had highly ramified morphology indicating it corresponded to active microglia (Parachikova et al., 2007). On the contrary, hippocampal sections immunostained for both MHC II and $A\beta_{1-42}$ and analyzed by confocal microscopy showed several clusters of cells which were immunopositive for both MHC II and $A\beta_{1-42}$ in mild to moderate AD cases (Parachikova et al., 2007). More importantly, this increase negatively correlated with learning and memory abilities in humans as measured by MMSE (Parachikova et al., 2007). Control non-demented brains present low MHC class II immunoreactivity that is indicative of low levels of microglia activation. Recently a study investigated the role of a decrease in the number of T-cells in AD pathology (Liu et al., 2014). They injected Aβ peptide into the hippocampus of BALB/c wild-type and BALB/c-nude mice with T-cell immunodeficiency ($n = 6$/condition) (Liu et al., 2014). The immunohistochemical analysis of the brain showed that the decrease in T Cells in the BALB/c-nude mice correlated with a deficit in neurogenesis and the expression of inflammatory markers. These authors concluded that T cells are required to promote hippocampal neurogenesis and that the decrease in T cells observed in AD brains may restrict neuronal regeneration in the hippocampus (Liu et al., 2014).

### 1.4. Role of glia activation in Alzheimer's disease pathology

#### 1.4.1. Microglia

Astrogliosis and microgliosis have been found always present in brains of AD patients (Beach et al., 1989; Brun and Englund, 1986; Mancardi et al., 1983; Overmyer et al., 1999). Glial cells significantly change morphology and functional properties during aging and under pathological situations, (Benarroch, 2013). Microglia represent about 10% of the cells in the CNS and is the first line of response against pathogens or other causes of brain injury. After activation microglia migrate and clear cell debris around damaged tissue. In AD as well as in other neurodegenerative conditions is evident the accumulation of activated microglia expressing MHC II within and around deposits of aggregated Aβ in the brain (McGeer et al., 1988; McGeer and McGeer, 1995, 2013; Rogers et al., 1988). It has been proposed that microglia have a key role removing Aβ plaques in AD brains (Sha et al., 2014). For example, it has been shown that activation of microglia inhibited Aβ neurotoxicity in a mouse model of AD (Simard and Rivest, 2006). In fact, it has been reported that when microglia cells are cultured in the presence of cortical slices from AD brains, they accumulate over the Aβ deposits and clear them (Bard et al., 2000). However, it is considered that microglia cannot efficiently degrade Aβ aggregates in aged brains. Leading to the speculation that senile plaque accumulation in AD brains may be caused by a deficient capacity of microglia to phagocyte Aβ plaques in the elderly (Majumdar et al., 2008; Paresce et al., 1997; Streit and Xue, 2014). A recent report showed evidence obtained using high-resolution confocal microscopy and *in vivo* two-photon imaging in AD mouse models, supporting the view that microglia constitute a barrier preventing outer $A\beta_{42}$ plaque expansion leading to condensed plaque micro-regions AD (Condello et al., 2015). In this report the authors showed that areas uncovered by microglia were less compact resulting in the formation of areas accumulating $A\beta_{42}$ protofibrills and more severe axonal dystrophy. They hypothesized that in aged Tg AD mice, a reduction in microglia results in more severe neuritic dystrophy (Condello et al., 2015). Furthermore, they showed that anti-Aβ immunotherapy increased microglia coverage and decreased neuritic dystrophy. The authors postulated that a failure of microglia activation and function is a characteristic contributing to AD development and that microglia may constitute a novel therapeutic targets for AD (Condello et al., 2015). In general, this evidence suggests that microglia may induce both neuroprotective and deleterious effects in the brain, with this depending on temporality and magnitude of their activation as well as the nature of the mediators they release. For example, upon nicotinic receptor stimulation, microglia release small amounts of tumor necrosis factor (TNF), which protect neurons, whereas lipopolysaccharide (LPS) stimulates a massive TNF release from these cells leading to neuroinflammation (Suzuki et al., 2006).

Macrophages can be divided in M1 and M2, according to its effect of inflammation and the factors that they express and release. For example, the macrophages type M1 are considered pro-inflammatory because they release factors that further enhance the inflammatory response and the oxidative stress in the brain such as the inducible nitric oxide synthase (iNOS), IL-1, IL-6, IL-12 and the tumor necrosis factor alpha (TNF-α). On the other hand the macrophages type M2 release anti-inflammatory factors such as the IL-4, IL-10, IL-13 and TNF-β (Wyss-Coray, 2006;

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Wyss-Coray et al., 2001a; Wyss-Coray and Rogers, 2012). Almost 30 years ago that active microglia cells were detected in the cortex of AD patients, (Luber-Narod and Rogers, 1988; Rogers et al., 1988). AD brains showed intensive microglia activation and increased expression of the neurothrophic factor kappa B (NFκB) and its downstream pro-inflammatory factors such as cytokines, and chemokines to name a few.

Abundant evidence *in vivo* suggests that these inflammatory factors might be critical contributors to the pathology of AD (Akiyama et al., 2000; Buckwalter and Wyss-Coray, 2004; Buttini et al., 1998; Dhib-Jalbut et al., 2006; Luo et al., 2007; Wyss-Coray, 2005, 2006; Wyss-Coray et al., 2001a,b; Wyss-Coray and Mucke, 2000, 2002; Wyss-Coray et al., 2002) as well as in other neurodegenerative conditions such as HIV dementia (Rostasy, 2005), Parkinson's disease (PD)(Miklossy et al., 2006) and multiple sclerosis (MS) (Inglese et al., 2005; Lassmann, 2007; Miklossy et al., 2006).

After several years of research, the most generally accepted view is that microglia cells are the resident macrophages mediating most of the innate neuroinflammatory responses in the brain contributing to exacerbate brain injury in many neurodegenerative disorders. New microscopic studies have permitted to visualize how microglia can efficiently and constantly survey their environment. Microglial cells extend processes several millimeters in their brain environment to detect changes in glial, endothelial and/or neuronal cells (Davalos et al., 2005; Nimmerjahn et al., 2005; Raivich, 2005). In the last decade, based on new experimental evidence, it has been proposed that microglia activation may have a dual role in the CNS, one neuroprotective and another mediating neurotoxicity (Yong, 2010; Yong and Marks, 2010). The potential beneficial effects of the activation of some of the neuroinflammatory factors such as ILs may reside on their ability to stimulate the expression of neurotrophic factors. For example, after brain trauma ILs induce an increase in the level of the member of the gp130 family of cytokines, the cilliary neurothrophic factor (CNTF) which has a neuroprotective effect (Nimmerjahn, 2009). These neurothrophic factors stimulate regeneration and constitute a negative feedback mechanism directed to inhibit the inflammatory response. For example, it has been reported that inhibition of microglia activation reduced brain damage after ischemic brain injury (Lalancette-Hebert et al., 2007). Gliosis in AD pathology not only involve microglia. It is well know that other glial cells such as astrocytes and oligodendrocytes are also affected and play a role during neuroinflammation as reviewed below in the following sections.

### 1.4.2. Astrocytes

Astrocytes are formed by a heterogeneous population of cells that includes astrocytes of the grey and white matter, radial astrocytes of the retina and cerebellum, velate astrocytes of the cerebellum and olfactory bulb. These cells differ in morphology as well as physiological properties such as membrane potential, ions conductance, and protein profile expression (Nimmerjahn, 2009). Astrocytes are tightly interconnected to neuronal function by regulating neuronal glucose metabolism, ion homeostasis, oxidative stress synaptic plasticity and the uptake and release of neurotransmitters (Nimmerjahn, 2009). Astrocytes normally have at least one projection contacting a basal lamina around blood vessels (Simard et al., 2003). Staggeringly, it has been estimated that a single gray matter astrocyte can contact thousands or millions of neuronal synapses. Similar to microglia, astrocytes activation can have beneficial and deleterious consequences (Sofroniew and Vinters, 2010). Astroglyosis has been observed around plaques deposits postmortem in humans AD brains and transgenic mouse models of AD (Rodriguez et al., 2009). The expression of GFAP (a marker of astrocytes) is inversely related with increasing Braak stages (Simpson et al., 2010). It has been shown that astrocytes activate by exposure to aggregated form of the Aβ increasing the expression and release of inflammatory factors such as IL-1β, IL-12 INF-γ, inducible nitric oxide (NO) synthase (iNOS), NO, and TNF-α (White et al., 2005). This increase seems to be mediated by the activation of transcription factors controlling the expression of these factors such as NFκB and CCAAT/enhancer binding protein, C/EBP. For example, NFκB is activated in astrocytes after exposure to Aβ (Bales et al., 1998).

Astrocytes express numerous receptors that have been postulated to bind to Aβ including the receptor-like protein, the membrane-associated proteoglycans, receptors for advanced glycation endproducts (RAGEs), low density lipoproteins, insulin degrading enzyme and scavenger receptor-like receptors. A previous study showed that α7nAChRs are well expressed on the surface of hippocampal astrocytes and current evidence suggests that they can uptake and clear Aβ. For example, It has been reported that exposure to $A\beta_{1-42}$ (200 nmoles/L) significantly increased the expression of GFAP in cultured hippocampal slices and hippocampal astrocytes (Nagele et al., 2003; Wyss-Coray et al., 2003). Also, Aβ exposureinduced the release of several inflammatory factors, such as the macrophage inflammatory protein 1alpha (MIP1α, RANTES, IL-1β, IL-6, and TNF-αto the astrocytes culture media. More importantly, pre-treatment with nicotine (10 μM) attenuated Aβ pro-inflammatory effects.

In addition to astrocytes, also the neutrophils are considered key players inducing neuronal damage by generating toxic free radicals, proteases and pro-inflammatory cytokines such as IL-1β and the TNF-α (Shaftel et al., 2007). The migration of neutrophils into the brain is facilitated by BBB dysfunction that is associated with activation of proteases, such as matrix metalloproteinases (MMPs) MMPs especially MMP-9 (Kamat et al., 2014). Neurons and glia synthesize MMPs that stimulate the release numerous pro-inflammatory factors such as CXCL-8, IL-1β and TNF-α. MMPs breakdown the collagen type IV of basal membranes disrupting the blood–brain barrier (BBB). This barrier regulates CNS homeostasis, cerebral blood flow and synaptic activity (Lok et al., 2012; McCarty, 2009).

The activation of astrocytes and increase in MMP activity may lead to both dysregulation of cerebral blood flow and a decrease in the availability of energy supplies to neurons (Aliev et al., 2003). These changes may finally result in a deficit in synaptic plasticity and general brain function in AD (Seo et al., 2012). However, the inhibition of MMP-9 would have deleterious effects as this protease is actively engaged in synaptic remodeling. β-dystroglycan (β-DG), a trans-membrane protein, is a synaptic target for MMP-9 which is cleaved upon neuronal stimulation (Gorkiewicz et al., 2010; Michaluk and Kaczmarek, 2007; Michaluk et al., 2007).

Also, calcineurin, a calcium-dependent phosphatase, is increased in reactive astrocytes in AD brains (Foster et al., 2001; Norris et al., 2002, 2005). Calcineurin stimulates the activation and translocation to the nucleus of the transcription factor named nuclear factor of activated T-cells (NFAT). The translocation of NFAT resulting in a decrease in the expression of the glutamate transporter 2, provoking a decrease of glutamate uptake and increased apoptosis due to glutamate excitotoxicity (Abdul et al., 2009).

IFN-γ-mediated neuroinflammation also seems to affect the evolution of Aβpathology in transgenic (Tg) mice. Expression of mIFN-γ in brains of APP TgCRND8 mice provoked microglia and astrocytes activation and a significant decrease in Aβ deposition. IFN-γ increased the expression of multiple glial activation markers and components of the complement cascade as well as promoted the infiltration of peripheral monocytes to the brain. Since IFN-γ did not affects APP or Aβ levels, it has been postulated that IFN-γ expression suppresses Aβ deposition by enhancing insoluble Aβ clearance by phagocytosis (Rodriguez et al., 2009)

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*1.4.3. Oligodendrocytes*

Also oligodendrocytes seems to be affected by AD pathology (Whitman and Cotman, 2004). Oligodendrocytes produce myelin, which envelopes axons and is critical for neurotransmission. Several lines of evidence have shown lesions and myelin abnormalities in the white matter such as well as demyelination of axons around plaques in the gray matter of AD brains (Carmeli et al., 2013; Desai et al., 2010; Lloyd et al., 2001; Mitew et al., 2010; Wang et al., 2012; Xu et al., 2014). Furthermore, cytotoxicity studies have shown that Aβ peptides reduce oligodendrocyte viability (Lee et al., 2004; Roth et al., 2005; Xu et al., 2001). Also, it has been observed that Aβ oligomers inhibit myelin sheet formation during the differentiation of Oligodendrocytes precursor cells (Horiuchi et al., 2012). The triple Tg AD mice (3xTg-AD mice) expressing mutants forms of the human APP, presenilin and Tau (P301L), show significant alterations in overall myelination and oligodendrocyte integrity (Desai et al., 2010). These changes in oligodendrocytes function appeared before Aβplaques and Tau pathology suggesting that the demyelination process is an early event during the progress of AD (Desai et al., 2010).

*1.5. Role of glia activation in Tau pathology*

On the other hand, AD mouse models have consistently shown a development of both astrogliosis and microgliosis induced by accumulation of aggregate forms of Aβ in the brain. Actual evidence strongly suggests a role for microglia and astroglia in Aβ-induced Tau-phosphorylation (Ghosh et al., 2013). In addition, microglia may stimulate both Aβproduction and Tau up-regulation (Garwood et al., 2011; Lee et al., 2015; Saez et al., 2006; Saez et al., 2004).

Tg mice developing Tau pathology has been created. These models, express mutant human tau genes (P301S or P301L) that are associated with the development of frontotemporal dementia (FTD), a neurodegenerative disease characterized by prominent taoupathy (Nacmias et al., 2014). These mice progressively develop NFT and motor abnormalities (Arendash et al., 2004; Gotz et al., 2001, 2010, 2012; Pooler et al., 2013; Xia et al., 2015). Tau-pathology is dramatically aggravated by inflammation of the CNS and parallels with the activation of astrocytes and microglia cells (Garwood et al., 2011; Ghosh et al., 2013; Kitazawa et al., 2011; Lee et al., 2015). Rodent models combining Aβ and Tau pathology has been created such as the regulatable transgenic mouse rTg3696AB expressing both human APP(NLI) and tau (P301L) driven by the $Ca^{2+}$/calmodulin-dependent protein kinase promoter. These mice developed Aβplaques, NFT, and neurodegeneration (Paulson et al., 2008). Using this animal model, it was shown that LPS-induced inflammation exacerbated tau pathology in the brain (Lee et al., 2010). Also, a triple Tg mouse line (3xTg-AD), carrying PS1 (M146V), APP(Swe) and Tau (P301L) human transgenes has been produced. These 3xTg-AD mice progressively develop, intracellular Aβ accumulation, plaques and NFT as well as synaptic deficits before plaque and tangle pathology (Arendash et al., 2004; Ishizawa et al., 2003; Oddo et al., 2003). Recently, however, a new rat model of AD has been created expressing both the FAD APPswe and presenilin 1 (PS1-dE9) genes. These rats showed Aβ plaques followed by tau tangles as well as neurodegeneration and memory deficits (Cohen et al., 2013). Alternative mRNA splicing, generates from a single tau gene six brain tau proteins. The differences among these six brain tau isoforms result from the presence of three (3R tau) or four (4R tau) repeats of 31or 32 amino acids in the carboxy-terminal end of each of two sets of these proteins, as well as from the occurrence of inserts of 29 or 58 amino acids or no insert at all in the amino-terminal region, derived from alternative splicing of exon 10 (E10). The authors argued that rats developed NFT naturally, because at difference with mouse, rat Tau biology is much closer to human. Rats possess the same number of tau isoforms than humans, while mice express only three isoforms because of the lack of exon 10 splicing. The analysis of activated microglia and astrocytes by immunohistochemistry revealed a significantly increase in reactive microglia and astroglia as early as 6 months of age in Tg *vs.* non-Tg rats, prior to significant Aβ deposition but concurrent with increased oligomeric Aβ levels (Cohen et al., 2013). The authors pointed out that coherent with a role of clearance of plaques by microglia, they observed neuronal nuclei (NeuN) deposits within the cytoplasm of microglia cells. As previously discussed, glia activation induces the release of pro-inflammatory factors such as IL-1β and may be a key contributing factor inducing tau pathology. The hypothesis that neuroinflammatory factors contribute to tau dysregulation, is supported by evidence showing that blocking of IL-1β signaling with an antibody against the IL-1β receptor decreased Tau-pathology in the triple transgenic mice (Kitazawa et al., 2011), while increasing IL-1β levels instead promoted Tau-pathology (Ghosh et al., 2013). Preventing Tau hyperphosphorylation can be a critical therapeutic goal in delaying or halting the progression of AD. Complement activation is an important inflammatory event which causes neuronal injury in AD brains through formation of the membrane attack complex. Interestingly, aggregated Aβis a potent activator of human complement but not of mouse complement (McGeer and McGeer, 2010).

## 2. Nicotinic acetylcholine receptors activation and neuroinflammation in AD

In the CNS the heteromeric α4/β2 and homomeric α7 receptors are the largest number of nAChRs (Dineley et al., 2015). As previously mentioned, α7nAChRs channel open with very low probability, and, is easily desensitized by agonists, in a reversible manner (Uteshev et al., 2002). The α4nAChRs instead open with high probability but relax into high affinity desensitized states (D) in an almost irreversible manner. α7nAChRs are expressed by neurons from regions that have been involved in working memory and primarily affected by AD such as the hippocampus and prefrontal cortex.

It has been known for many years the anti-inflammatory effects of α7nAChR stimulation in conditions of sepsis, such as the ACh-induced attenuation of the release of TNF, IL-1β, and IL-6 by macrophages (Galvis et al., 2006). The presence of cholinergic anti-inflammatory pathways mediated by α7nAChR in the brain, offers new therapeutic avenues for AD and others neurological disorders that are characterized by neuroinflammation. In neurons, the α7nAChRs regulate the presynaptic release of several neurotransmitters and signaling pathways in the postsynaptic sites promoting neuronal survival and synaptic plasticity. The study of the role of α7nAChRs in microglial/macrophage cells has been facilitated by the fact that from the receptors sensitive toα-bungarotoxin (α-BTX), only α7 receptors are expressed in monocytes and macrophages (Wang et al., 2003). The α7nAChR activation by nicotine and other of its agonists is thought to decrease the abnormal activation of microglia. It is considered that Nicotine's suppressive effects on microglia activation, mediate some of the neuroprotective actions of nicotine against AD and PD (Barreto et al., 2015). The activation of the inflammatory response is highly regulated and implies sophisticated signaling mechanisms. For example, The Toll-like receptors (TLRs) are a family of proteins that trigger the innate immune response to pathogens (Hedayat et al., 2012; Miyauchi et al., 2012; Saiga et al., 2012; Takeda and Akira, 2001, 2004a,b; Takeuchi et al., 1999a,b). TLRs recognize specific pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS) from the bacteria envelope, and activate signaling pathways leading to increased levels of pro-inflammatory cytokines (Takeda

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et al., 2003). The activity of the TLRs are negatively regulated by several signaling factors including MyD88, IL-1 receptor-associated kinase-M (IRAK-M), the myeloid differentiation primary response, PI3K/Akt, suppressors of cytokine signaling 1 and 3 (SOCS-1, SOCS-3) and Signal transducer and activator of transcription 3 (STAT3). Importantly, from the regulators analyzed so far, STAT3, SOCS-3, PI3K and MyD88s have also been implicated in mediating the anti-inflammatory effect of the α7nAChRs in immune cells. The participation of IRAK-M, is yet to be evaluated (Maldifassi et al., 2014).

### 2.1. Nicotine

Nicotine is an agonist of α7nAChR which activation triggers inward rectification currents due to increased $Na^+$ and $Ca^{2+}$ permeability at the presynaptic site. These currents depolarize the cell, open voltage-activated $Na^+$ and $Ca^{2+}$ channels and activate different signaling cascades as well as. Moreover, $Na^+$ and $Ca^{2+}$ currents depolarize the presynaptic membrane, and consequently activate voltage-gated $Ca^{2+}$ channels as well as $Ca^{2+}$-dependent $Cl^-$ and $K^+$ currents, inducing neurotransmitter release. This mechanism has been demonstrated at cholinergic, dopaminergic, gabaergic, glutamatergic, noradrenergic, and dopaminergic synapses (Posadas et al., 2013).

Nicotine is anti-inflammatory and reduces lipopolysaccharide (LPS)-induced TNF-α release from microglia without affecting its mRNA expression (De Simone et al., 2005). Also, it has been shown evidence that nicotine moderately decreases the release of nitric oxide (NO) and IL-10 while increasing the expression of COX-2 and prostaglandin $E_2$ ($PGE_2$) in microglia (De Simone et al., 2005). The inhibition of LPS-induced TNF release by nicotine has been shown to be accompanied by the inhibition of c-Jun kinase (JNK) and p38 MAP kinases, which are involved in the post-transcriptional stages of TNF synthesis. They also found evidence suggesting that α7nAChRs in microglia increase intracellular $Ca^{2+}$ levels by stimulating signaling processes involving the activation of phospholipase C and $Ca^{2+}$ release from intracellular stores, rather than functioning as a conventional ion channels (Suzuki et al., 2006). These results opened the discussion whether the activation of the nAChRs by nicotine can be used to alleviate neurological conditions showing neuroinflammation such as AD, Parkinson's disease (PD) and HIV-1 infection (Chang et al., 2010). However, the use of nicotine or other compounds for the activation of the nAChRs to reduce inflammation in immunocompromized individuals is a complex subject.

Of major relevance are the potential beneficial consequences of reducing inflammation by stimulating the nAChRs. For example, the activation of these receptors can prevent or ameliorate several brain functions affected by AD and other neurological disorders. Several lines of evidence have shown that activation of α7nAChRs improves attention, and learning and memory in rodents and non-human primate models of several neurological and psychiatric disorders including schizophrenia (Jones et al., 2012; Leiser et al., 2009; Lieberman et al., 2013; Winterer et al., 2013; Young and Geyer, 2013) and AD (Alkadhi et al., 2011, 2010; Carson et al., 2008; Chen et al., 2006; Leiser et al., 2009; Nordberg et al., 2002; Srivareerat et al., 2011; Uteshev et al., 2003).

In addition, neuroprotective effects of nicotine against Aβ fibrils (Kihara et al., 1998; Ono et al., 2002, 2006; Salomon et al., 1996; Zamani and Allen, 2001) and oligomers have been well documented (Inestrosa et al., 2013). Aβ oligomers concentration correlates better with synaptic dysfunction and memory impairment in AD than the number or size of senile plaques in the brain. The effect of nicotine on both soluble Aβ oligomers toxicity in hippocampal neuronal cultures and memory performance of APP/PS1 mice, has been investigated (Inestrosa et al., 2013). Chronic treatment with nicotine prevented cognitive impairment in both young and old APP/PS1 transgenic mice. The activation of α7nAChR by nicotine stabilized β-catenin, was neuroprotective against Aβ oligomer-toxicity in both pre- and postsynaptic sites, and prevented both early postsynaptic and late presynaptic damage as well as the Aβ-induced loss of β-catenin by a mechanism dependent on the receptor activation (Inestrosa et al., 2013). Moreover, activation of the canonical Wnt/β-catenin signaling induced an up-regulation of α7nAChR expression. Nicotine improved working memory in APP/PS1Tg mice before widespread senile plaque development, but also in mice with full pathology development (Inestrosa et al., 2013).

### 2.2. Positive allosteric modulators of the nicotinic receptors: Beneficial effects in reducing neuroinflammation in AD

A deficit in the expression of the α7nAChRs has been found involved in the etiology and development of AD and many others mental health conditions including the Tourette's syndrome, PD, bipolar disorder and schizophrenia. Unfortunately, the fact that α7nAChRs, become rapidly desensitized by its agonists has limited the benefits of drugs directed to increase the levels of ACh such as the Acetylcholinesterase inhibitors (AChEI) as well as agonists and partial agonists binding to the canonical ACh binding site of these receptors (Williams et al., 2011). α7nAChRs are activated by conformational changes induced by ligands such as competitive antagonists, full and partial agonists that bind the receptor at the classical agonist binding site (orthosteric). However, α7nAChRs also are positively or negatively regulated by allosteric modulators that bind not to the orthosteric but allosteric sites. The mechanism of action of allosteric modulators has been very well discussed by several authors based in the classical model of protein allostery described by Monod, Wyman, and Changeux (MWC) (Changeux et al., 1998; Changeux and Edelstein, 1998, 2005; Monod et al., 1965; Williams et al., 2011). Briefly, an allosteric modulator would change the conformation of the receptor in a way that would enhance the representation of receptors in functional states, permitting higher rates of spontaneous openings in the absence of orthosteric agonist. Also, allosteric modulators of α7nAChRs will increase the efficacy of agonists to induce cation currents throughout the activated channel by decreasing the desensitized states of the receptors. PAMs are thought may switch the receptor's conformation from non-activatable to activatable states.

Interestingly, zinc, which level increases during aging, inhibits α7nAChR-mediated responses with an $IC_{50}$ of 27 μM in a voltage-insensitive manner (Palma et al., 1998). PAMs, such as SB-206553 (3,5-dihydro-5-methyl-*N*-3-pyridinylbenzo [1,2-b:4,5-b′] -dipyrrole-1 (2H)-carboxamide) and PNU-120596 (1-(5-chloro-2,4-dimethoxy-phenyl)-3-(5-methyl-isoxazol-3-yl)-urea) enhance agonist-evoked α7 currents in hippocampal neurons (Dunlop et al., 2009; Hurst et al., 2005) and glial cells in acute brain slices (Lopez-Hernandez et al., 2009; Velez-Fort et al., 2009). PNU-120596 at micromolar concentrations enhanced the α7nAChRs-dependent release of dopamine induced by agonists in the prefrontal cortex *in vivo* (Livingstone et al., 2010).

In contrast to agonists of the receptors, PAMs will facilitate the intermittent activation of the receptor by its natural agonists (Gatson et al., 2015; Monod et al., 1965). Furthermore, as a new approach, new PAMs of these receptors have been developed to prevent α7nAChR desensitization induced by agonist drugs.

The study of α7 receptor responses to agonists measured from transfected cells and *Xenopus laevis* oocytes revealed that desensitization of these receptors is nearly immediate and the probability for α7nAChR channel to open after agonist application is only 0.002. In presence of higher concentration of the agonists this receptor is converted to a ligand-bound non-conducting state.

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However, this state can be destabilized by PAMs such as PNU-120596 (Williams et al., 2012).

Since α7 receptors have high calcium permeability, a potential negative side effects induced by persistent calcium increase inside brain cells should be also considered. Persistent and higher $Ca^{2+}$ currents can become toxic to cells expressing this receptor. Interestingly has been found that the potentiating effect of PNU-120596 is highly dependent on temperature and has a reduced effect at normal body temperatures. The authors postulated that the use of type II PAM inhibiting the receptor desensitization, may potentially put cells expressing high levels of α7-nAChRs, such as hippocampal neurons, at risk (Williams et al., 2012). Thus, our ideal drug against AD may reduce the time of desensitization but not totally block the transition of the receptor to less sensitive states. However, as discussed in the last section, the characterization of the safety of these compounds in clinical studies has not shown significant negative side effects induced by PAMs. Nevertheless, it is important to keep in mind that different modulatorsofα7nAChRs may elicit different effects than nicotine over innate immune cells. For example, it has been found that the α7nAChR PAM GTS-21 (3-(2,4-dimethoxybenzylidene anabaseine) does not decrease LPS-induced release of the pro-inflammatory cytokine TNF-α by cultured microglia. Similarly, GST-21 did not decrease cytokine production by human monocytes that were activated by ligands of Toll-like receptor (TLR)2, TLR3, TLR4, TLR9, and RAGE (Rosas-Ballina et al., 2009; Thomsen and Mikkelsen, 2012). However, GTS-21 has a prominent immune-modulator effect in several models of inflammatory disease (Pavlov et al., 2003, 2007). Paradoxically, both methyllylcaconitine an α7nAChR antagonist and its weak agonist NS6740 (<10%) reduced LPS-induced TNF-α release, indicating that α7nAChR antagonism also can induce anti-inflammatory effects on microglia (Thomsen and Mikkelsen, 2012). Based on this evidence, it was suggested that the anti-inflammatory effects of nicotine may be not the result of the activation of α7nAChRs and that antagonism of these receptors can also reduce neuroinflammation (Thomsen and Mikkelsen, 2012). The assumption of other related mechanisms is supported by evidence showing alternative or linked mechanisms. In one study from Suzuki et al. (2006), it was found that nicotine enhanced P2X(7) receptor-mediated TNF release, at the same time as suppressing LPS-induced TNF release in rat primary microglia (Suzuki et al., 2006). Nicotine elicited a transient increase in intracellular $Ca^{2+}$ levels, which was abolished by specific blockers of α7nAChRs. However, this response was independent of extracellular $Ca^{2+}$ and blocked by U73122, an inhibitor of phospholipase C (PLC) and xestospongin C, a blocker of the IP3 receptor.

Other studies have investigated the effect of PAMs over the activation of apoptotic signaling mechanisms that are triggered by oxidative stress. In one of these studies, cultured human umbilical vein endothelial cells were treated with $H_2O_2$ (400 μM) or $H_2O_2$ plus PNU-282987 (10 μM). Cell viability and membrane integrity were measured. Also the expression of the apoptotic factors bcl-2, bax, cleaved capase-3, the apoptosis inducing factor (AIF), vascular peroxidase-1 (VPO-1) and phospho-JNK were investigated (Li et al., 2014). The PAM, PNU-282987 prevented $H_2O_2$-induced apoptosis and intracellular oxidative stress. In addition, PNU reduced the increase of VPO-1 and JNK1/2 phosphorylation induced by oxidative stress. Pre-treatment with methyllycaconitine blocked the cytoprotective effect of PNU-282987 (Li et al., 2014). Since AD is characterized by oxidative stress and mitochondrial dysfunction in the brain (Kosenko et al., 2014; Perry et al., 2000), it is possible that PAMs also may have an effect decreasing the consequences of oxidative stress in the brain.

### 2.2.1. Cotinine a positive allosteric modulator of the nAChRs

We have previously reported two studies showing the effect of cotinine in a Tg mouse model of AD, expressing five familial AD mutations (FAD): PSEN1 (M146L), PSEN1 (L286V), APP (K670N/M671L)(Swedish), APP(I716V) (Florida), and APPV717I (London). These mice (Tg6799, 5xFAD) exhibit many AD pathology characteristic including intraneuronal Aβ accumulation, plaque development, reduction in PSD95 levels (Shao et al., 2011), Tau hyperphosphorylation (Saul et al., 2013), memory deficits and non-cognitive symptoms such as depressive-like behavior (Oakley et al., 2006). We found that cotinine administered before (2 months of age) (Echeverria and Zeitlin, 2012; Echeverria et al., 2011) or after the appearance of Aβ plaques and cognitive decline (4–5 months of age) (Patel et al., 2014), improved working and reference memory, reduced plaque burden and depressive-like behavior in the Tg6799 mice. In addition, at a molecular level, cotinine activated Akt, inhibited GSK3β and increased the expression of the postsynaptic density protein 95 (PSD95). A decrease of PSD95 levels that is considered a biomarker of postsynaptic degeneration was previously found in the Tg6799 mice (Oakley et al., 2006).

Respect to potential pharmacodynamic effects of cotinine, it was puzzling that the initial evidence showed that cotinine was a very poor agonist of α7nAChRs; However, all our neurochemical, pharmacological and behavioral data suggested that cotinine elicited α7nAChRs signaling. This evidence suggested that cotinine was a PAM of the α7 receptor. Recently, it has been shown data, using electrophysiological techniques to analyze the activity of α7nAChRs expressed in *Xenopus* oocytes, suggesting that S-cotinine is a α7nAChR PAM inhibiting the receptor desensitization while enhancing its activation by ACh. The authors supported our hypothesis that cotinine should be beneficial as an adjunctive therapy to the AChEI for the treatment of AD (Terry et al., 2015).

A previous study working with primary monocytes isolated from whole human blood, demonstrated that pre-treatment with cotinine for two hours inhibited the inflammatory response to gram negative bacteria and dramatically suppressing the production of cytokines such as TNF (EC50 = 100 ng/mL, 0.3 μM). Cotinine blocked more than 80% of the release of TNF-α induced by *Pheudomona gingivalis* (MOI = 10). This effect was suppressed by α-BTX (2 μg/mL) suggesting that this effect was mediated by α7nAChRs. This effect was dependent on PI3K activity and was accompanied by Akt activation and the inhibition of GSK3βby phosphorylation at Serine 9 (Akt phosphorylation site). This is interesting because a similar activation of Akt and inhibition of GSK3β was found by us in brain homogenates from cotinine-treated Tg6799 mice. Cotinine's anti-inflammatory effect was independent of NFκB but it was accompanied by the stimulation of IL-10 release (Rehani et al., 2008). Cotinine's anti-inflammatory effects involved the activation of TLRs. In fact, in monocytic cells, cotinine suppressed the cytokine production resultant upon agonist-specific engagement of the TLRs (TLR 2/1; 2/6; 4 and 5) (Bagaitkar et al., 2012). Cotinine offers many advantageous characteristics to other PAMs for the therapy of AD, including its anti-Aβ aggregation activity, anti-inflammatory actions, no addictive properties, good solubility in water, long plasma half-life and non-significant toxicity in humans. However, clinical investigations are required to demonstrate its effectiveness against AD.

The activation of α7nAChRs by nicotine has been associated with the enhancement of cell proliferation of non-small cell lung cancer and malignant pleural mesothelioma (Brown et al., 2012). Interestingly, a recent study investigated the effect of cotinine (18 and 36 ng/mL) or vehicle on the viability of non-small-cell lung cancer line A549. Cell viability and intracellular architecture was assessed using electron and fluorescent microscopy. Cotinine altered the cytoskeleton, at least in part by affecting the organization of F-actin and induced A549 cell death. The authors concluded that cotinine, by affecting F-actin, may influence the size and shape of non-small-cell lung cancer cells, which may

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undergo death through apoptotic and mitotic catastrophe pathways after exposure to cotinine. Few *in vivo* studies suggest an anti-tumorigenic effect of cotinine. One study evaluated the effect of cotinine and nicotine-*N*′-oxides on tumor development in F344 rats initiated with *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) (LaVoie et al., 1985). Six-week-old rats, were administered FANFT for a month, post-treated with water, cotinine, trans-nicotine-*N*′-oxide, or a mixture of cis-nicotine-*N*′-oxide plus trans-nicotine-*N*′-oxide in the drinking water for 78 weeks, and tumor development in bladder was evaluated. Rats treated with FANFT showed increased incidence of mesothelioma of the peritoneum and thyroid tumors. Cotinine, trans-nicotine-*N*′-oxide, and the mixture of cis- and trans-nicotine-*N*′-oxides were neither carcinogens nor promoters of urinary bladder tumors in rats initiated with FANFT. Similarly, FANFT-induced tumorigenesis in the tongue and palate was not affected by cotinine-treatment or the other cotinine metabolites.

The antioxidant and anti-inflammatory effects of cotinine may have beneficial effects against malignancy. However, more *in vivo* studies are required to investigate its effect in specific type of tumor or cancer cells.

Despite, many other α7nAChRs PAM have been discovered, only few of them have been characterized *in vivo* and/or have intrinsic characteristic that make them suitable for therapeutic use including long plasma half-life, and low toxicity and cost. Cotinine has these desired characteristic but may have similar limitations that have been discussed for other α7nAChRs PAMs. For example, for cotinine to have therapeutic value sufficient concentrations of both ACh and nAChRs need to be present. Considering the slow progression of AD, this limitation does not seems an insurmountable problem such the prevention of cholinergic deterioration can be achieved by treatment at early or middle stages of the pathology. This is particularly true recently due to the accelerated development of new detection methods to assess amyloid and Tau pathology. Also, new mechanisms mediated by other neurotransmitters receptors may contribute to the beneficial effects of cotinine. Cotinine stimulates the release of serotonin (Echeverria and Zeitlin, 2012; Fuxe et al., 1979) and dopamine in the brain (Dwoskin et al., 1999) likely due to the modulation of the nicotinic receptors that modulate the release of these neurotransmitters in the brain (Guo et al., 2012).

### 2.2.2. Galantamine

Galantamine is an AChEI that also acts as a PAM of the nAChRs (Maelicke et al., 2001; Samochocki et al., 2000). Galantamine was initially described as a potent "allosteric potentiating ligand (APL)" of human α3/β4, α4/β2, and α6/β4 nAChRs, and of the chicken/mouse chimeric α7/5-hydroxytryptamine 3 receptor. Galantamine (16 to 24 mg/day) potentiated agonist responses of nAChRs at low micromolar concentrations (i.e., 0.1–1 μM). However at higher doses (>10 μM), galantamine inhibited these receptors (Samochocki et al., 2003). Structural data showed that galantamine binding site is different from the ACh binding site. But also showed that both sites are in close proximity facilitating the synergistic interaction between these sites in the positive activation of the receptor (Ludwig et al., 2010). Similar to cotinine, galantamine is an alkaloid extracted from plants that is neuroprotective (Kihara et al., 2004), and inhibits Aβ aggregation. Interestingly, galantamine stimulates the enhancing effect of Aβ clearance by microglia (Takata et al., 2010). Long-term treatment with galantamine delayed the progression of cognitive decline and behavioral symptoms, in patients with moderate or advanced forms of the disease (Aronson et al., 2009; Feldman et al., 2009a,b; Kavanagh et al., 2011a,b,c). Studies using the 5XFAD Tg mouse to investigate the effect of galantamine on AD pathology, including neuroinflammation, showed that chronic oral treatment with galantamine improved the performance of the Tg mice in behavioral tests, measuring anxiety such as open field and light-dark avoidance, when compared to controls. In addition, galantamine reduced both amyloid burden and gliosis (14–24 mg/kg) (Bhattacharya et al., 2014).

Unfortunately, Galantamine induces undesired side effects similar to other cholinergic drugs such as gastrointestinal symptoms and new therapies or forms of delivery to reduce the side effects are currently been investigated (Bhattacharya et al., 2015; Maelicke et al., 2010).

### 2.2.3. Anatabine

Also the effect of anatabine another alkaloid present in plants of the Solanacea family, on microglia activation has been investigated (Paris et al., 2013). Anatabine, which has a similar chemical structure to nicotine, also has anti-inflammatory effects in cellular models of LPS-induced toxicity. Anatabine prevented the activation of the transcription factors STAT3 and NFκB induced by LPS in neuronal cell lines and human microglia. *In vivo* anatabine inhibited cytokine production (IL-6, IL-1β and TNF-α) in the plasma, kidney and spleen of animals injected with LPS and concomitantly opposed STAT3 phosphorylation induced by LPS in the spleen and kidney. Furthermore, chronic treatment with anatabine, reduced TNF-α, IL-6 levels and STAT3 phosphorylation in the brain of Tg APPsw mice when compared to control Tg mice (Paris et al., 2013).

## 2.3. Managing the inflammatory response as a therapeutic strategy for Alzheimer?

In the last 30 years, the development of treatments for AD has largely based on the "cholinergic hypothesis" of AD (Appel, 1981; Bartus et al., 1982; Craig et al., 2011; Nagai et al., 1983; Rossor, 1983; Struble et al., 1982). This hypothesis states that central cholinergic transmission dysfunction is the main contributing factor leading to neurodegeneration in AD. In this regard, the progressive loss of nicotinic receptors in AD brains was described (Whitehouse et al., 1986, 1988).

Current pharmacologic treatments of AD include the use of AChEIs to inhibit ACh degradation, and memantine a NMDA receptor antagonist directed to reduce the glutamate neurotoxicity. The AChEIs such as donepezil (Courtney et al., 2004) and rivastigmine (Birks et al., 2000, 2009) grants only symptomatic short-term benefits without stopping the progression of AD. Unfortunately, despite its limitations these drugs are the only available therapies, because all new disease-modifying drugs that have been tested failed to improve cognitive abilities in phase 3 clinical trials. These studies thought us that reducing oxidative stress or neuroinflammation or removing senile plaques, although necessary, are not sufficient as a single strategy to halt the progression of AD (Ghezzi et al., 2013).

Numerous evidence has been reported suggesting that chronic inflammation may be the common and more relevant factor supporting the development and progression of AD (Mushtaq et al., 2015). Consistent with this hypothesis, epidemiological studies have shown that non-steroidal anti-inflammatory drugs (NSAIDs) consistently reduce the risk of AD (Blain et al., 2000; Hoozemans et al., 2003; McGeer et al., 1996, 2006; Zandi et al., 2002). However, so far, these drugs have proven to be an ineffective treatment in clinical trials. A recent meta-analysis of seven clinical trials investigating the effectiveness of the NSAIDs diclofenac/misoprostol, nimesulide, naproxen, rofecoxib,ibuprofen, indomethacin, tarenflurbil, and celecoxib in improving memory, were reported (Miguel-Alvarez et al., 2015). The results of cognitive performance assessed using the Scale–cognitive subscale (ADAS–cog), the Clinical Dementia Rating Scale sum of boxes (CDRSOB), and the

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mini-mental state examination (MMSE), showed no statistical or clinical significance of NSAIDs treatment compared with placebo in AD progression (Miguel-Alvarez et al., 2015). The reason for this failure has been attributed to the dose and its use at advanced stages of the pathology (Miguel-Alvarez et al., 2015).

Thus in AD brains some molecular mechanisms of neuroinflammation may promote the development or progression of AD, whereas other can be neuroprotective. Altogether, this evidence suggests that part of the inflammatory response can be beneficial to reduce brain injury but a persistent and uncontrolled response may be highly detrimental to neuronal survival and brain functions.

Thus the question still remains, how to positively manage the inflammatory pathways to prevent or treat this devastating pathology?. Based on these ideas immunotherapy has been proposed for the treatment of AD (Villoslada et al., 2008). Immunotherapy has been extensively investigated as a therapeutic approach to clear aggregated forms of $A\beta_{42}$, and/or hyperphosphorylated forms of Tau in AD brains. However, this exciting area of research, has encountered many difficulties derived from the fact that triggering an immune response against an endogenous epitope may induce undesired adverse autoimmune reactions that can become even fatal. In fact, immunization with Aβ reduced amyloid deposits and reduced memory and learning deficits in animal models leading to a great excitement in the biomedical community. As it is well known, promising clinical trials of active immunization with Aβ were halted because 6% of the treated patients developed meningoencephalitis which was presumably induced by a T cell-mediated autoimmune response (Orgogozo et al., 2003). The analysis of the brains from immunized patients indicated that the $A\beta_{42}$ immunotherapy had reduced $A\beta_{42}$ burden but it did not stop the progression of the cognitive impairment (Boche et al., 2008; Holmes et al., 2008; Nicoll et al., 2003, 2006). To abolish the autoimmune T cell responses elicited by the $A\beta_{42}$ peptides, most of the following immunization trials have been performed using B cell epitopes (Aβ1–6, or Aβ 1–15) to produce antibodies. Three of these B cell epitopes vaccines for active immunizations, CAD106, ACC001 and Affitope, are currently in Phase 2 clinical trials.

These efforts have been followed by new attempts to develop safe approaches such as the passive immunizations with antibodies against different regions of the Aβ which are currently in several stages of clinical trials. In passive immunotherapy anti-$A\beta_{42}$ antibodies are injected intravenously to facilitate the phagocytosis of amyloid by microglia, to inhibition amyloid aggregation, or to sequester the peptides to induce a positive efflux of $A\beta_{42}$ from brain. Unfortunately, some of the monoclonal antibodies (mAbs) used induced vasogenic edema and brain microhemorrhage. The monoclonal antibody therapies, Solanezumab from Lilly, Crenezumab from Genentech, and Gantenerumab from Hoffmann La Roche have been subjected to clinical trials. Solanezumab and Crenezumab are humanized mouse mAbs detecting a mid-region Aβ epitope, $A\beta_{13-28}$ and $A\beta_{12-23}$, respectively. The preclinical studies of the solanezumab showed an impressive increase in plasma Aβ levels in the PDAPP Tg mice (DeMattos et al., 2001). Similarly, a phase II randomized, double-blind, placebo-controlled clinical trial, investigating the effect of solanezumab on the progression of AD in participants at mild-to-moderate stages of the pathology, showed a significant increase in $A\beta_{42/40}$ levels in plasma and CSF (Farlow et al., 2012). However, a report from a phase 3 clinical studies (ClinicalTrials.gov NCT00905372 and NCT00904683.) indicated that Solanezumab, failed to improve cognition or functional ability in the AD patients (de la Torre, 2014; Doody et al., 2014; Laske, 2014; Salloway et al., 2014). It was argued that some methodological issues could be affecting the results obtained, for example, in both phase 3 clinical trials testing solanezumab and bapineuzumab, a quarter of patients lacked fibrillar amyloid pathology at baseline. So a new third phase 3 clinical trial for solanezumab, called Expedition 3, in patients with mild AD was started (Hu et al., 2015).

In the report at the Alzheimer's Association International Conference 2014, it was disclosed that the Phase 2 results for crenezumab, the Genentech's antibody, tested in the mild to moderate ABBY trial were negative overall, with modest benefits in patients with mild AD. In a different Phase 2 trial (BLAZE) including 91 participants with mild to moderate AD, the participants received either placebo, or crenezumab (15 mg/kg) for 73 weeks. The effect of treatment on Aβ burden was evaluated using Positron emission tomography (PET) imaging by measuring the retention of the amyloid ligand PiB. The amyloid imaging using PET did not reveal differences in amyloid burden between treatment groups (Ostrowitzki et al., 2012).

On the other hand, Gantenerumab is the first fully human anti-Aβ mAb directed to both N-terminal and central regions of Aβ. 2 to 7 infusions of intravenous gantenerumab (60 or 200 mg) or placebo every 4 weeks were investigated. Gantenerumab (200 mg) resulted in a reduction of insoluble Aβ deposits in the brains (Ostrowitzki et al., 2012). A 6-month PET study in 16 AD patients showed that gantenerumab reduced brain Aβ burden, possibly stimulating microglial-mediated phagocytosis. Two phase 3 trials of gantenerumab in AD patients with mild dementia are currently being performed. Also, there is an ongoing prevention trial testing the use of gantenerumab in presymptomatic subjects with genetic mutations for autosomal-dominant AD (Panza et al., 2014).

In 2012, Biogen Idec started a current, clinical trial study (BIIB037), using a human IgG1 monoclonal antibody against a conformational epitope found on Aβ. This trial tested the efficacy of aducanumab in 160 people with prodromal or mild AD, in a multicenter setting. No outcome data of this trial have been formally reported. However, in December of 2014, Biogen announced its decision to move into Phase 3 based on interim data suggesting Aβ lowering and cognitive benefits. The trial is expected to end in 2016.

At the preclinical level, one of the latest studies reported the development of a vaccine based in an artificial peptide corresponding to ten repeats of $A\beta_{3-10}$ fragments. The authors said that these constructs elicited high titers of antibodies reacting against monomeric, oligomeric and fibrillar forms of $A\beta_{42}$ peptide. In addition, these antibodies reacted with the Aβ plaques, reducing its deposition. Despite microglia activation was lower than with other antibodies, it was nevertheless sufficient to efficiently remove the Aβ plaques. No obvious signs of abnormal inflammation such as T cell and Prussian blue positive cell were found, suggesting that T cell infiltration and micro-hemorrhage were minimal using this vaccine. Future studies will be required to confirm the usefulness of this strategy in humans (Sha et al., 2014).

In addition new strategies of immunization to target tau pathology has been developed (Boutajangout et al., 2010; Lambracht-Washington and Rosenberg, 2013). Passive immunization with the well-characterized mAb PHF directed against phosphorylated forms of tau, and MC1, recognizing an early pathologic conformational epitope on Tau, showed, similarly to the active immunization, a significant reduction in tau pathology (Asuni et al., 2007). Astrogliosis was observed in mice with abundant NFT after active immunotherapy suggesting that the mechanism underlying this effect involved the clearance of NFT by activated astrocytes.

Since an increase in Tau concentrations has been observed in blood from tau immunized mice, it is feasible that similar to anti-Aβ immunizations, another mechanism that may be involved in the reduction of NFT in the brain is the clearance of tau from the brain into the periphery, (Bi et al., 2011; Boimel et al., 2009; Boutajangout et al., 2011; Rosenmann et al., 2006; Troquier et al., 2012).

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**Table 1**
Main findings regarding the effect(s) of cholinergic agents with anti-inflammatory properties in Alzheimer's disease.

| Compound | Amyloidosis/ tauopathy | Attention/ memory | Neuronal survival | Neuroinflammation | Citation(s) |
|---|---|---|---|---|---|
| Anatabine | ↓Aβ levels and tau pathology | | | ↓ Neuroinflammation[a] | Paris et al. (2013) |
| Cotinine | ↓Aβ aggregation[a] | ↑ Attention ↑ Memory[a] | ↑Neuronal survival[a] | ↓ Neuroinflammation[a] | Rehani et al. (2008), Bagaitkar et al. (2012) |
| Galantamine | ↓Aβ aggregation | ↑ Attention [a] ↑Memory[a] | | ↓Neuroinflammation | Lenzken (2007), Matharu (2009), Aronson et al. (2009), Feldman et al. (2009a,b), Kavanagh et al. (2011a–c) |
| Nicotine | ↓Aβ β aggregation ↑Tau phosphorylation | ↑Attention ↑Memory[a] | ↑Neuronal survival[a] | ↓Neuroinflammation[a] | Kihara et al. (1998), Ono et al. (2002, 2006), Salomon et al. (1996), Zamani and Allen (2001), Inestrosa et al. (2013) |
| NSAIDs Diclofenac, Misoprostol, Nimesulide, Naproxen, Rofecoxib, Ibuprofen, Indomethacine, Tarenflurbil, Celecoxib | | Nonclinical effects | | | Miguel-Alvarez et al. (2015) |

[a] Animal studies.

Interestingly, it has been observed that immunization against Aβ induces a reduction of GSK3β Tau kinase and Tau phosphorylation. Using a post-mortem cohort of immunized AD cases, the effect of Aβ immunization on GSK3β expression was assessed. 11 immunized and 28 unimmunized AD cases were investigated for active, inactive and total GSK3β levels. All brain regions analyzed showed a significant decrease in the three forms of GSK3β in the immunized AD cases compared to the unimmunized AD cases. This data suggested a link between Aβ pathology, GSK3β and tau pathology (Amin et al., 2014).

One explanation for the failure of active and passive immunotherapy is that anti-Aβ antibodies may damage the cerebral vasculature already affected by Aβ deposition.

Fc gamma receptors (FcγR) are a family of immunoglobulin (Ig)-like receptors which bind to the Fc portion of IgG, and mediate the response of effector cells to immune complexes. Both mouse and human studies showed evidence suggesting that activation of FcγR by therapeutic antibodies during immunotherapy may trigger deleterious pro-inflammatory responses affecting the vasculature. FcγR expression on microglia and neurons seems to increase with age exacerbating this effect. Thus, FcγR stimulation in the CNS, either by endogenous IgG or therapeutic antibodies, may damage the vasculature and contribute to the neurodegenerative process (Fuller et al., 2014).

Altogether, most evidence (Table 1) argues in favor of a combined therapeutic approach to diminish the negative side effects of neuroinflammation but taking advantage of its beneficial effects.

## 3. Conclusions

In light of all evidence, it is reasonable to propose that more of one aspect of AD pathology including the cholinergic deficit, neuroinflammation, and neuronal loss as well as Aβ and tau abnormal aggregation, may need to be targeted simultaneously to observe beneficial effects in the affected individuals. The positive advances in the use of immunotherapy against AD are promising in showing less toxic side effects, however still show limited efficacy. New approaches including the use of modulators of the nAChRs in conjunction with current and new multi-target therapies are urgently needed to delay the appearance or halt the progression of AD in a timely manner.

## Author contributions

All authors participated in drafting and revising the manuscript for intellectual content.

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