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Alpha7 nicotinic acetylcholine receptor: A link between inflammation and neurodegeneration

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Abstract

Alzheimer's disease (AD) is the leading cause of dementia affecting over 25 million people worldwide. Classical studies focused on the description and characterization of the pathological hallmarks found in AD patients including the neurofibrillary tangles and the amyloid plaques. Current strategies focus on the etiology of these hallmarks and the different mechanisms contributing to neurodegeneration. Among them, recent studies reveal the close interplay between the immunological and the neurodegenerative processes. This article examines the implications of the alpha7 nicotinic acetylcholine receptor (alpha7nAChR) as a critical link between inflammation and neurodegeneration in AD. Alpha7nAChRs are not only expressed in neurons but also in Glia cells where they can modulate the immunological responses contributing to AD. Successful therapeutic strategies against AD should consider the connections between inflammation and neurodegeneration. Among them, alpha7nAChR may represent a pharmacological target to control these two mechanisms during the pathogenesis of neurodegenerative and behavioral disorders.

Keywords

Inflammation; Neurodegeneration; Alzheimer's disease; Microglia; Beta amyloid; Tau; Nicotinic receptors; Alpha7nicotinic receptors; Acetylcholine

1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia worldwide and the seventh leading cause of death in 2004 killing over 65,000 patients in the USA. AD is the third most costly disease with an annual national cost of $100 billion and an average lifetime cost of care of nearly $175,000 per patient (Smith, 1998). Over 5 million Americans are currently afflicted with AD, and the number of individuals over 65 with AD is estimated to reach 16 millions in USA by 2050 (http://www.alz.org/national/documents/Report_2007FactsAndFigures.pdf). AD is a neurodegenerative disorder characterized by widespread cognitive impairments that begin with episodic memory declines. As the neurodegenerative disorder progresses, AD is characterized by a progressive cognitive impairment that extends to the domains of language

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(aphasia), skilled movements (apraxia), recognition (agnosia), and executive functions (such as decision-making and planning).

The typical hallmarks of AD include the neurofibrillary tangles and amyloid plaques that represent the two characteristic pathological processes of the disease: hyperphosphorylation of tau and misfolding of amyloid beta (Fig. 1). AD is considered a tauopathy due to abnormal aggregation of the tau protein in the brain (Rubio et al., 2006;Tolnay and Probst, 1999). Tau is a microtubule-associated protein that stabilizes the microtubules and contributes to the cellular transport of vesicles along the neurites. Like most microtubule-associated proteins, the binding of tau to microtubules is regulated by phosphorylation. Hyperphosphorylation of tau in AD patients favors its dissociation from the microtubules and its accumulation in paired helical filaments (PHFs) (Kosik et al., 1986;Wolozin et al., 1986). PHFs aggregate into detrimental clusters inside nerve cell bodies known as *neurofibrillary tangles* (NFTs) and dystrophic neurites associated with amyloid plaques. In addition to this process, the massive dissociation of tau from microtubules interferes with the axonal transport, contributing to the loss of synapses and neuronal degeneration correlated with the characteristic cognitive impairments of AD (DeKosky and Scheff, 1990;Terry et al., 1991). AD is also associated with the accumulation of abnormal folded amyloid beta$_{1–42}$ (Aβ42) in the extracellular senile plaques. Aβ42 results from the abnormal proteolysis of the transmembrane amyloid beta precursor protein (APP) by the β- and γ-secretases (Wilson et al., 1999). The causative role of the amyloid in AD is based on its increased production and its early deposition in brain plaques of individuals with familial AD caused by mutations in APP, presenilin 1 (PS1) and PS2 genes (Selkoe, 1998). However, the extent of amyloid beta accumulation does not correlate well with pathogenesis (Slow et al., 2006) and there are a significant number of individuals with amyloid plaques who do not suffer dementia. Actually, soluble amyloid beta correlates better with the cognitive decline of AD patients than the insoluble, fibril deposits (Cleary et al., 2005). In APP transgenic models, neurological deficits precede the deposition of significant amounts of Aβ42, suggesting that the pathophysiology of AD may occur prior to amyloid deposition (Westerman et al., 2002).

The development of successful therapeutic strategies for AD is limited by our understanding of the pathological processes and the contribution of immunologic mechanisms to the pathogenesis. This article analyzes the contribution of inflammatory processes to neurodegeneration and whether anti-inflammatory strategies may provide a beneficial effect against AD. A classical example is that nicotine was used to compensate the loss of cholinergic neuron observed in the frontal cortex of AD patients, and administration of nicotine to AD patients reduced anxiety and improved cognitive performance in clinical trials (Levin et al., 2006). However, nicotine does not only target cholinergic receptors in neurons but it also controls the immune responses in glia cells. Thus, it may not be surprising that the *alpha7 nicotinic acetylcholine receptor* (*alpha7nAChR*), the receptor proposed for treatment of AD, is the same receptor that appears to mediate the anti-inflammatory potential of nicotine in glia cells. Here, we discuss the implications of alpha7nAChR as a critical link between inflammation and neurodegeneration, and its potential pharmacological implications for the treatment of AD.

2. Cholinergic implications in neurodegenerative disorders: from acetylcholine to nicotinic receptors

Cognitive impairments in AD patients are mainly characterized by the loss of cholinergic neurons, which are the most affected in the disease. In the central nervous system (CNS), acetylcholine (ACh) has a variety of effects as a neuromodulator involved in synaptic plasticity and stability. Acetylcholine enhances the amplitude of synaptic potentials following long-term potentiation (LTP) in many regions of the brain but mainly in the neocortex, CA1, dentate

gyrus and piriform cortex. Acetylcholine receptors (AChRs) decrease the conductance of voltage-gated and Ca^{2+}-dependent currents. There are two types of acetylcholine receptors, muscarinic (mAChRs) and nicotinic receptors (nAChRs). Neuronal mAChRs are metabotropic receptors stimulated by acetylcholine and muscarine but blocked by atropine. They belong to the G-protein coupled family of receptors, and they also activate other ionic channels via a second messenger cascade. For instance mAChR can activate M_1, M_3, M_5 via phospholipase C or inhibit M_2, M_4 via adenylate cyclase. The nicotinic receptors (nAChRs) are cation-selective, ligand-gated ion pentameric channels composed out of selected alpha and/or beta subunits. To date, 12 neuronal subunits have been described including nine alpha (α2–α10) and three beta (β2–β4) subunits. The alpha subunits contain two adjacent cysteine residues for the binding of acetylcholine, whereas the beta subunits lack them (Alkondon and Albuquerque, 1993; Lukas et al., 1999). The combination of these subunits defines the function and affinity of the receptor for specific ligands (Sudweeks and Yakel, 2000). Nicotinic receptors are stimulated by acetylcholine and nicotine, but blocked by curare, α-conotoxin, α-bungarotoxin or mecamylamine (Itier and Bertrand, 2001). Both muscarinic and nicotinic acetylcholine receptors are not specific of the central system as they also appear in the peripheral nervous system.

Among the nAChRs, the alpha7nAChR has major clinical and pharmacological implications for AD. The alpha7nAChR is a homomeric pentameric ligand-gate ion channel with five acetylcholine binding sites (Drisdel and Green, 2000). Originally described as a sodium channel, the alpha7 subunit presents a high conductance for calcium (Berg and Conroy, 2002), low sensitivity to acetylcholine (Clarke, 1992) and a high affinity for α-bungarotoxin (Marks and Collins, 1982; Rangwala et al., 1997). This receptor also appears to trigger alternative signal pathways in neuronal and non-neuronal cells. In neuronal cells activation of the alpha7nAChR causes an increase in intracellular Ca^{2+} directly through voltage activated channels (activation of ERK1/2 in a Ca^{2+} and PKA dependent manner) (Dajas-Bailador et al., 2002b) and indirectly from intracellular sources following nicotinic ryanodine receptor channels activation (Dajas-Bailador et al., 2002a). In astrocytes, the alpha7nAChRs appears to modulate Ca^{2+} release from intracellular stores (Sharma and Vijayaraghavan, 2001). In neurons, nicotinic-induced increase in intracellular Ca^{2+} modulates glutamate and GABA activity (Maggi et al., 2001; Radcliffe and Dani, 1998) and regulates CREB, the transcription factor involved in the formation of the LTP (Lynch, 2004; Silva et al., 1998) via glutamatergic transmission (Hu et al., 2002).

Alpha7nAChRs are widely distributed in brain. Radioligand binding of [I^{125}] α-bungarotoxin shows a high to moderate even distribution of the alpha7nAChR in the CA1 region of the hippocampus and entorhinal cortex (Court et al., 2000). In the prefrontal and the motor cortex, the alpha7nAChR localizes in the pyramidal neurons of the layers II/III, V and VI (Wevers et al., 1994). Alpha7-mRNA has high and intermediate expression in the nucleus reticularis and lateral/medial geniculate bodies as opposed to the low expression in the thalamus (Breese et al., 1997; Court et al., 2000; Rubboli et al., 1994; Spurden et al., 1997). Basal ganglia has high expression of alpha7nAChR in substantia nigra, intermediate in caudate and putamen, and a lower expression in striatum (Court et al., 2000). Cerebellum exhibits strong expression of alpha7nAChR in selectively Purkinge cells and shows higher density in the molecular than in the granular layer (Court et al., 2000).

Decline in nicotinic receptors, particularly the alpha7nAChR in the frontal cortex, is associated with aging (Utsugisawa et al., 1999). Radioligand binding of [I^{125}] α-bungarotoxin to samples from patients ages 20–100 years old (Court et al., 1997) and 65–80 years old (Nordberg and Winblad, 1986) show significant reductions in the entorhinal cortex and the thalamus. No changes were observed in hippocampus (ages 20–100) or putamen (ages 22–80) (Court et al., 1997; Utsugisawa et al., 1999). Decline in nAChRs, including the alpha7nAChR, is also

associated with AD. These deficits appear early in the disease and correlate with the progressive loss of cognitive abilities (Nordberg, 1994, 2001; Whitehouse and Kalaria, 1995). In AD patients, the alpha7nAChRs protein levels are reduced in the cortex and hippocampus (Burghaus et al., 2000; Guan et al., 2000; Martin-Ruiz et al., 1999; Nordberg, 2001; Wevers et al., 2000). Although the protein loss is evident in AD, reductions in gene expression at the transcriptional level are less clear. The 36% reduction in alpha7nAChR-protein levels in the hippocampus of patients with AD (Guan et al., 2000) contrast with the 65% increase in alpha7nAChR-mRNA expression reported (Hellstrom-Lindahl et al., 1999). Apparent contradictory results were also found in the frontal cortex of AD patients showing no differences in [I^{125}] α-bungarotoxin binding (Davies and Feisullin, 1981; Sugaya et al., 1990), or a significant reduction of the alpha7nAChR-protein expression levels (Engidawork et al., 2001). These apparent contradictions may suggest a compensatory mechanism at the transcriptional level in both the cerebral cortex and the hippocampus (Nordberg, 2001). In conclusion, one of the major features in AD is the decline of nAChRs in disease-relevant brain regions such as the cerebral cortex and the hippocampus. This loss may be explained by the loss of cholinergic cells, which contribute to the cognitive dysfunction.

3. Alpha7nAChR and information processing

CHRNA7 knock out mice have cognitive dysfunction, including attention and working memory deficiencies (Fernandes et al., 2006; Hoyle et al., 2006; Young et al., 2007). Likewise, there is general consensus that the alpha7nAChR plays an important role in information processing in humans. In a series of studies Freedman and colleagues demonstrated that variants in the CHRNA7 gene influence susceptibility to schizophrenia and that the alpha7nAChR is involved in attentional gating as measured by the P50 ERP paradigm (Freedman et al., 2006; Martin et al., 2004). In this paradigm abnormalities in the alpha7nAChR system result in failures to reduce amplitude to the second auditory stimulus of a pair, a finding which suggests a basic defect in the filtering of novel from non-novel events. Furthermore, a specific alpha7nAChR agonist (GTS21) improved cognition in schizophrenia, including attention, working memory, speed and total score of a brief cognitive screening instrument (Olincy et al., 2006). P50 inhibition also improved. More detailed information on this area is available in several recent reviews (Levin, 2002; Martin et al., 2004; Potter et al., 2006).

4. Epidemiological implications of nicotine in neurodegenerative disorders

Epidemiological studies show that nicotine decreases the risk for Parkinson's disease (PD) and AD (Fratiglioni and Wang, 2000). This negative association is in agreement with postmortem studies showing diminutions of amyloid plaque deposits in former smokers with AD (Hellstrom-Lindahl et al., 2004b). Nicotine treatment appears to interfere with the formation of the amyloid plaques *in vitro* and *in vivo* (Hellstrom-Lindahl et al., 2004a; Ono et al., 2002; Utsuki et al., 2002) and to reduce the accumulation of insoluble Aβ42 peptides (Nordberg et al., 2002) through a mechanism mediated by alpha7nAChRs as shown with mecamylamine that blocks the increase of sAPP produced by treating SH-SY5Y neuroblastoma cells with nicotine (Hellstrom-Lindahl et al., 2004a). Several clinical trials indicate that chronic administration of nicotine in individuals with age-associated memory impairments and AD improves cognition in attention but not in memory (Snaedal et al., 1996; White and Levin, 1999, 2004; Wilson et al., 1995). Similar studies indicate that ABT418, a nicotinic alpha4beta2-agonist, improves memory and learning skills in AD patients (Potter et al., 1999). Nicotine also improves cognition in patients with psychiatric disorders such as schizophrenia where the loss of alpha7nAChRs may contribute to neurocognitive and sensory gating deficits (Adler et al., 1998; Depatie et al., 2002; Harris et al., 2004; Myers et al., 2004; Smith et al., 2002, 2006). Smoking improved auditory sensory gating in schizophrenic patients (Adler et al., 1993) and these effects appear to be mediated by the alpha7nAChR as shown by using alpha-

bungarotoxin and tubocurarine in rat hippocampus (Adler et al., 1998; Luntz-Leybman et al., 1992). The effects of smoking in memory remain controversial due to studies with negative (Depatie et al., 2002; Harris et al., 2004) and positive results (Myers et al., 2004). In conclusion, for both schizophrenia and AD, nicotine improves performance in attention through the alpha7nAChRs, while memory improvements seem to be driven through the alpha4beta2-nAChRs.

Nicotine seems to protect against the development of AD and PD through anti-inflammatory mechanisms. Both AD and PD are characterized by local inflammatory responses sustained by activated microglial cells. Nicotine induces anti-inflammatory mechanisms that diminish local inflammatory responses (Hellstrom-Lindahl et al., 2004a; Streit, 2002; Wang et al., 2000a, b). Among other, nicotine abrogates the production of TNF in culture of microglia through a mechanism dependent on ERK and p38 MAPK (Shytle et al., 2004; Suzuki et al., 2006). Experimental models of AD indicate that alpha7nAChR is the central core of the nicotine-mediated neuroprotection. Nicotine decreases accumulation of beta-amyloid in the cortex and hippocampus of APP (V717I) transgenic mice. These studies also indicate that nicotine prevents the activation of the NF-κB and c-Myc pathways by inhibiting the ERK and p38 MAPK kinases via alpha7nAChRs (Liu et al., 2007). This mechanism of the alpha7nAChR function was confirmed by using RNA interference in the experiments of nicotine-mediated neuroprotection. However, nicotine also has other beneficial effects on AD that are not mediated through the alpha7nAChRs. For instance, nicotine appears to protect the neuron cell against the Aβ42 toxicity by scavenging ROS and NO free radicals (Liu et al., 2003; Liu and Zhao, 2004), chelating copper and iron (Bridge et al., 2004; Zhang et al., 2006) and protecting antioxidants in cells (Linert et al., 1999; Liu et al., 2003).

5. Inflammation in neurodegenerative disorders

Activated microglia increase in aging brain and are associated with degenerative disorders such as AD, Parkinson and amyotrophic lateral sclerosis (ALS). Microglia exert neuroprotective functions by secreting growth factors or diffusible anti-inflammatory mediators, which help to resolve inflammation and restore tissue homeostasis (Klegeris and McGeer, 2002; Streit, 2002). However, microglia can also be neurotoxic by producing free radicals, inflammatory cytokines and other toxic factors. Recent studies indicate that neurons and astrocytes can regulate innate immune responses in microglia via both alpha7nAChRs and purinergic $P2X_7$ receptors (Shytle et al., 2004; Suzuki et al., 2006). Primary cultures of both resting and actívate microglia and astrocytes show choline acetyltransferase (ChAT) activity and synthesize acetylcholine (De Rosa et al., 2005) suggesting that this neurotransmitter act as a local immune regulator and contribute to the regulation of microglial functions.

Stimulation of purinergic $P2X_7$ receptors on microglia by neuronal released ATP induces small TNF production, which protects neurons (Zhang et al., 2007). On the other hand, LPS-stimulated microglia causes massive TNF production leading to inflammation (Suzuki et al., 2006). Acetylcholine and nicotine inhibit the production of TNF in LPS-stimulated mouse microglial cultures (De Rosa et al., 2005; Shytle et al., 2004). This anti-inflammatory potential of acetylcholine and nicotine is based on the inhibition of the NF-κB pathway through a specific `nicotinic anti-inflammatory pathway' dependent on the alpha7nAChR (Wang et al., 2004). The inhibition of TNF production in LPS-stimulated microglial cultures is also associated with a reduction in the activation of ERK and p38MAPK (Shytle et al., 2004; Suzuki et al., 2006) (Fig. 2). P38MAPK expression appears restricted to neurons and glial cells containing hyperphosphorylated tau, as well as dystrophic neurites of senile plaques in AD (Pei et al., 2001). P38MAPK phosphorylates tau *in vitro* at the threonine 181 and serines 202, 396 and 422 with different efficiencies for particular sites (Buee-Scherrer and Goedert, 2002; Ferrer et al., 2005; Goedert et al., 1997) (Fig. 3). Thus, inhibition of p38MAPK prevents tau

phosphorylation (Fig. 2). Nicotine also acts as an anti-inflammatory agent on microglia by increasing the expression of COX-2 and the synthesis of prostaglandin PGE_2, known to down-regulate microglial activation and expression of proinflammatory genes including TNF (De Rosa et al., 2005; Suzuki et al., 2006). However, nicotine has no effect on the release of IL-1β or IL-10, but it down-regulates nitric oxide (NO) production (Liu et al., 2007). The effect of nicotine on both, LPS-induced TNF production and PGE_2 release, is counteracted by alpha-bungarotoxin, the specific antagonist of the alpha7nAChRs.

Activated microglia in the brain colocalize with amyloid plaques (Akiyama et al., 2000) and facilitate amyloid clearance by a phagocytic response (Frautschy et al., 1992; Rogers et al., 2002). Activated microglia can also exacerbate tau pathology (Kitazawa et al., 2005; Li et al., 2003; Yoshiyama et al., 2007) through a mechanism dependent on the cdk5/p25 (Kitazawa et al., 2005) (Fig. 2). Brain microglia increase p25, a calpain-induced cleaved fragment of p35 that activates cdk5 (Humbert et al., 2000; Lee and Tsai, 2003). Cyclin-dependent kinase-5 (cdk5) then hyper-phosphorylates tau at the serines 202 and 235, representing the disease-associated phospho-epitopes recognizes by the antibodies AT8 and TG3 respectively (Noble et al., 2003; Sengupta et al., 1997). P35 localizes in the cell membranes meanwhile p25 localizes in the cytoplasm and nucleus (Lee and Tsai, 2003; Weishaupt et al., 2003) becoming a neurotoxic fragment implicated in neuronal apoptosis (Lee et al., 2000). Over-expression of p25 has been confirmed in the brain of AD patients (Patrick et al., 1999). In this sense, little is known about the regulation of cdk5 by nicotinic receptors. Recent studies indicate that nicotine inhibits cdk5 phosphorylation of DARPP-32 (dopamine- and cAMP-regulated phosphoprotein of 32 kDa) at threonine 75 neostriatal slices through a mechanism possibly mediated by alpha4beta2nAChRs (Hamada et al., 2005).

Various types of anti-inflammatory agents have been assessed in clinical trials for AD. Meta-analysis of studies of AD in relation to the use of NSAIDs have found no beneficial effect of NSAIDs in preventing cognitive decline (de Craen et al., 2005). Prednisone, a glucocorticoid that inhibits the induction of COX-2, was also ineffective in improving cognition in AD (Aisen et al., 2000). Likewise, randomized clinical trials with COX-2 inhibitors (e.g. Rofecoxib, Naproxen) have failed to improve cognition in patients with mild to moderate AD (Aisen et al., 2003; Reines et al., 2004). Certain NSAIDs, including ibuprofen, have differential mechanisms of action on the inflammatory response and deposition of beta-amyloid. Ibuprofen possesses preferential Abeta-42 lowering activity not related to the inhibition of cyclooxygenases, but altering gamma-secretase activity (Leuchtenberger et al., 2006; Weggen et al., 2001). Indomethacin, also shown to lower Abeta-42, stabilizes cognitive decline in clinical trials of AD patients, perhaps independently of its Cox-2 inhibitory properties (Rogers et al., 1993; Weggen et al., 2001). Negative studies may have resulted from use of NSAIDs relatively late in the disease process or imprecise targeting of the inflammation response.

6. Alpha7nAChR neurotoxicity and neuroprotection

Alpha7nAChR mediates the toxicity of the beta-amyloid 42 (Aβ42). Many studies indicate the direct binding of Aβ42 to the alpha7nAChR as a triggering factor of neuronal cell death and Alzheimer's pathology. The binding of Aβ42 to the alpha7nAChRs on the neuronal surfaces leads to internalization of the alpha7nAChR-Aβ42 complex and its accumulation within the lysosomal compartment (D'Andrea et al., 2001; Wang et al., 2000a, b). This alpha7nAChR-Aβ42 interaction inhibits acetylcholine release and calcium flux, and contributes to cell death suggesting that this interaction may be a key event in the pathogenesis of AD (Fig. 4). The most vulnerable neurons to neurodegeneration appear to be those that express the alpha7nAChR. Aβ42 first accumulates in these neurons producing cell death prior to plaque formation (D'Andrea et al., 2001; Gyure et al., 2001; Shie et al., 2003; Wirths et al., 2001). This mechanism (mediated via ERK1/2 signaling) links the amyloid and the cholinergic system

modulating synaptic plasticity and cognitive performance (Lynch, 2004; Silva et al., 1998). These results suggest that the alpha7nAChR could be a promising therapeutic target for treatment of AD. The Aβ42–alpha7nAChR interaction may induce tau phosphorylation at the Serine 202, Threonines 181 and 231 via ERKs and c-Jun N-terminal kinase (JNK-1) (Wang et al., 2003b) (Fig. 4). Alpha7nAChR gene delivery into mouse hippocampal neurons indicates that overexpression of alpha7nAChR prompted tau phosphorylation at both serine 202 and threonine 205 as recognized by AT8 (a monoclonal antibody that recognizes tau protein phosphorylated at these sites) (Ren et al., 2007) (Fig. 3). These studies depict the alpha7nAChR connecting the two classical pathological landmarks of AD beta-amyloid and hyperphosphorylation of tau, and support this receptor as a potential pharmacological target to inhibit tau phosphorylation in AD.

Alpha7nAChR-agonists trigger activation of tyrosine kinase Janus 2 (JAK2) and phosphorylation of Akt via activation of phosphatidylinositol-3-kinase (PI3K) (Kihara et al., 2001; Shaw et al., 2002) (Fig. 4). This mechanism seems to play a role in the neuroprotective properties of the alpha7nAChR versus amyloid neurotoxicity. In the neuronal cell line PC12, nicotine competes with Aβ42 for the binding to alpha7nAChR (in a “dominant” way), and prevents the Aβ42-induction of caspase 3 and apoptosis. The latter seems to be the result of nicotinic activation of the JAK2-PI3K-Akt signalling pathway, rather than blockade of Aβ42 binding to the alpha7nAChR (Shaw et al., 2002). This effect appears to be mediated by alpha7nAChR because the protection is blocked by alpha-bungarotoxin and is mimicked by the alpha7nAChR-agonist TC-1698 (Marrero et al., 2004; Shaw et al., 2002, 2003). Treatment with nicotine for ten days in the APPsw mice model (transgenic mice overproducing mutant amyloid β protein precursor, βAPP) reduced insoluble amyloid Aβ1–40 and Aβ1–42 peptides by 80% in the brain cortex of 9 month-old mice (Hellstrom-Lindahl et al., 2004a). This effect is mediated, at least in part, by the alpha7nAChRs as shown by using mecamylamine (Hellstrom-Lindahl et al., 2004a). Together, these findings support the notion that JAK2 mediates the alpha7nAChR-induced neuroprotection against Aβ42. Hence, these studies strengthen the potential of alpha7nAChR as a pharmacological target for neuroprotection in AD by preventing neuronal apoptosis.

7. Alpha7nAChR-agonists and allosteric modulators in neurodegenerative disorders

Alpha7nAChR-agonists were developed for the treatment of disorders with a cognitive component such as AD and schizophrenia despite early concerns that the rapid desensitization of this receptor would limit their therapeutical potential. One of the most characteristic alpha7nAChR-agonist is GTS21. GTS21 (3-[(2,4-dimethoxy) benzylidene]-anabaseine), a partial alpha7nAChR-agonist, enhances attention, working memory and episodic memory measured in healthy humans (Kitagawa et al., 2003). This compound was well tolerated at doses of up 450 mg/day, doses higher than those allowed by nicotine, and no significant side effects were observed. Unlike nicotine, GTS21 has no effect on locomotor activity in mice or on dopamine turnover in experimental rats indicating that it is less toxic than nicotine (Kitagawa et al., 2003; Meyer et al., 1998; Ulloa, 2005). A recent proof-of-concept trial indicate that GTS21 improve cognition and P50 sensory gating (a positive component of the auditory evoked potential peaking around 50 ms post-stimulus, which provides a measure of sensory motor gating) in schizophrenic patients (Martin et al., 2004; Olincy et al., 2006). Although the cognitive improvements were primarily in attention, further studies are needed to clarify if the improvements apply to other cognitive functions (e.g. immediate and delayed memory functions). Based in these initial results achieved with GTS-21, clinical trials in participants between 50 and 80 years old with AD were developed by Athenagen Biopharmaceuticals to evaluate both safety and cognitive improvements in these patients though results are not yet published. *In vitro*, GTS-21 can protect neurons against damage induced by amyloid peptides,

this is in agreement with previous studies suggesting that alpha7nAChRs can have a neuroprotective potential. GTS21 have three major adversities for clinical use: (1) GTS21 is not specific for alpha7nAChR and it affects other receptors including alpha4beta2-nAChRs (Gerzanich et al., 1995; Meyer et al., 1998; Stokes et al., 2004) and 5-HT_{3A} (Machu et al., 2001), (2) GTS21 has high affinity for the rodent receptor but it presents low affinity for the human alpha7nAChR (Gerzanich et al., 1995; Meyer et al., 1998; Stokes et al., 2004), and (3) GTS21 appears to have a limited brain penetration (Kem et al., 2004). These limitations appear to be overcome by a second generation of alpha7nAChR-agonists including 4OHGTS (3-(4-hydroxy, 2-methoxybenzylidene) anabaseine) (Meyer et al., 1998; Uteshev et al., 2003), compound that was developed to increase its affinity for human alpha7nAChR (Gerzanich et al., 1995). SSR180711 (1, 4-Diazabicyclo [3.2.2] nonane-4-carboxylic acid, 4-bromophenyl ester), was specifically design as a selective alpha7nAChR-agonist, which rapidly penetrates into the brain and displays high affinity for human alpha7nAChRs. Microdialysis studies show that administration of this compound increases acetylcholine release, glutamatergic neurotransmission and LTP in rat hippocampus in a dose-dependent manner (Biton et al., 2007). Thus, this new generation of alpha7nAChR holds high expectancies to improve cognitive deficits.

MEM 3454 (Memory Pharmaceuticals/Roche) is a novel partial agonist of the alpha7nAChR with 5-HT_3 receptor antagonist properties. MEM 3454 was developed as a potential therapy for AD and schizophrenia and it is currently in phase-II clinical trial. Results from phase I showed significant improvements of memory and concentration in healthy subjects after 13 days of daily 15 mgrs (Callahan et al., 2006), though the exact paradigm used to assess its effects were somewhat unveil. Quinuclidines are also partial alpha7nAChR-agonists (e.g., PNU-282987, Pfizer; PNU-282987 ([*N*-[(3R)-1-Azabicyclo [2.2.2] oct-3-*yl*]-4-chlorobenzamide hydrochloride])) that improve cognitive functions in experimental animals models (Bodnar et al., 2005; Leonik et al., 2007). A novel set of azabicyclic aryl amides to improve the properties of PNU-282987 were recently identified as selective alpha7nAChR-agonist with a potential for treating cognitive deficits (Walker et al., 2006). Among them, compound 14, *N*-[(3R)-1-Azabicyclo [2.2.2]oct-3-*yl*] furo [2,3-c] pyridine-5-carboxamide (14, PHA-543,613), presents improved oral bioavailability, brain penetration, efficacy improving auditory sensory gating and novel object recognition (Wishka et al., 2006). ABBF (Bayer group), *N*-[(3R)-1-azabicyclo[2.2.2]oct-3-*yl*]-7-[2-(methoxy)phenyl]-1-benzofuran-2-carboxamide, is also a novel agonist with higher affinity for the alpha7 receptor (no agonist activity at other nAChRs subtypes) and a better binding selectivity over the 5-HT_3 receptors, that improves working and recognition memory in rodents (Boess et al., 2007).

In addition to characteristic nicotinic agonists, the nAChR can be activated by a novel class of drugs, called allosteric enhancers because they activate these receptors without binding to the acetylcholine-binding site (Akk and Steinbach, 2005; Pereira et al., 2002). The most characteristic examples are physostigmine and galantamine (Reminyl; Janssen Pharmaceutica, Titusville, NJ); both belong to a class of acetylcholinesterase inhibitors approved for symptomatic treatment of schizophrenia and AD. These drugs presumably act by raising and prolonging the profile of acetylcholine via an inhibitory effect on the esterase. However, these drugs can also bind directly to nAChRs and modulate its activation. Galantamine produces a brief, voltage-dependent channel block, consistent with a simple, linear open channel blocking mechanism (Cooper et al., 1996). Galantamine does not interfere with the binding of nicotinic agonist such as acetylcholine, carbachol, choline or [I^{125}]-alpha-bungarotoxin (Akk and Steinbach, 2005). These acetylcholinesterase inhibitors have no significant effect on either the amplitude or kinetics of alpha7nAChRs activated by ACh, but they slowed the rate of (Fayuk and Yakel, 2004) recovery from desensitization through an indirect mechanism; responses activated with either choline or carbachol seem unaffected. The existence of multiple classes of binding sites is well established for other ligand-gated ion channels. For example, the

$GABA_A$ receptor can be activated by several classes of drugs that bind to no overlapping regions of the receptor: while GABA and muscimol interact with the characteristic ligand-binding site, barbiturates and steroids bind different domains (Ueno et al., 1997). Further studies are needed to identify the precise binding site of these potential allosteric enhancers to nAChRs, determine its pharmacological interest and contribution to the therapeutic effect of these compounds in AD. Future studies are needed to determine whether the cognitive potential of these agonists is based on their binding to neuronal receptors or whether their anti-inflammatory potential may contribute to their therapeutic potential in neurological disorders.

More selective allosteric enhancers for nAChRs are just starting to emerge. PNU-120596 is the first selective allosteric potentiator reported for the alpha7nAChR, with no effects on alpha4beta2, alpha3beta4 or alpha9beta10-nAChRs (Hurst et al., 2005), Compounds 2087101, 2087133 and 1078733 have been recently described as selectively potentiate alpha7, alpha2beta4, alpha4beta2 and alpha4beta4, but not alpha3- or alpha1-containing nAChRs or other ion channels (Broad et al., 2006). These compounds should be useful in establishing if nAChR potentiators can improve desensitization, have better tolerance, while producing comparable cognitive enhancement to the nAChR agonists. In addition, their selectivity potential for central nAChRs, but not ganglionic or neuromuscular nAChRs, may help to understand its clinical efficacy.

8. Concluding remarks and future directions

Recent studies suggest that cholinergic attrition associated with AD may actually link inflammation and neurodegeneration. Although acetylcholine is historically considered to be a neurotransmitter, it can also function as an immune cytokine and might represent a common ancestral mediator in cellular biology. Acetylcholine can be synthesized by both nervous and immune cells and serve as link for the neural-immune coordination (Ulloa, 2005). Deficiencies in the cholinergic system can explain cognitive impairments as well as a chronic inflammatory environment contributing to neurodegeneration. Chronic microglial activation contributes to neurodegenerative events such as plaque formation, dystrophic neurite growth and tau hyperphosphorylation. A recent study in a P301S tauopathy mouse model describes synaptic loss and microglial activation preceding tangle formation (Yoshiyama et al., 2007). Thus, microglia driven neuropathological responses constitute itself a pathogenic factor in neurodegenerative diseases such as AD. Among the cholinergic receptors, alpha7nAChR stimulation appears to be required for the anti-inflammatory potential of cholinergic agonists in immune cells including microglia. Giving this connection, it may not be surprising that nicotine and the alpha7nAChR have been extensively involved to the pathogenesis of AD. These studies suggest that the beneficial effects of nicotine in neurological disorders may be, at least in part, mediated by its anti-inflammatory role in microglia cells. Nicotine may impinge directly in both mechanisms. It can target neurons and improve cognitive performance, but it may also attenuate inflammatory responses in glial cells. This dual mechanism can explain some discrepancies found in the literature. Nicotine may prevent tau hyperphosphorylation *in vivo*, but not in neuronal cultures of cell lines. These discrepancies can be explained by the effects of nicotine in glial cells and warrant future studies in co-culture of glial and neuronal cells. Future studies are also needed to determine whether the cognitive potential of nicotinic agonists is based on its neuronal or anti-inflammatory potential.

Experimental evidence links the alpha7nAChR with inflammatory processes (Wang et al., 2003a). The alpha7nAChR expression is increased in astrocytes from hippocampus and entorhinal cortex of AD patients when compared with age-matched controls (Graham et al., 2002, 2003; Teaktong et al., 2003). It may represent a compensatory mechanism to restrain TNF production in astrocytes during AD. If so, alpha7nAChRs-agonists may provide a pharmacological strategy to restrain the production of inflammatory cytokines like TNF, but

also to selectively modulate the NF-κB pathway in immune cells (Huston et al., 2006). This pathway contributes to inflammatory responses in immune cells but it also has a neuroprotective potential in neurons. Little is known about the contribution of this pathway to AD, but this hypothesis is in agreement with studies in apoE4 mice indicating that the NF-κB pathway plays a critical role in neuroinflammation associated with AD (Ophir et al., 2005). Future studies are needed to determine whether alpha7nAChRs can induce a differential regulation of NF-κB in different cell lines.

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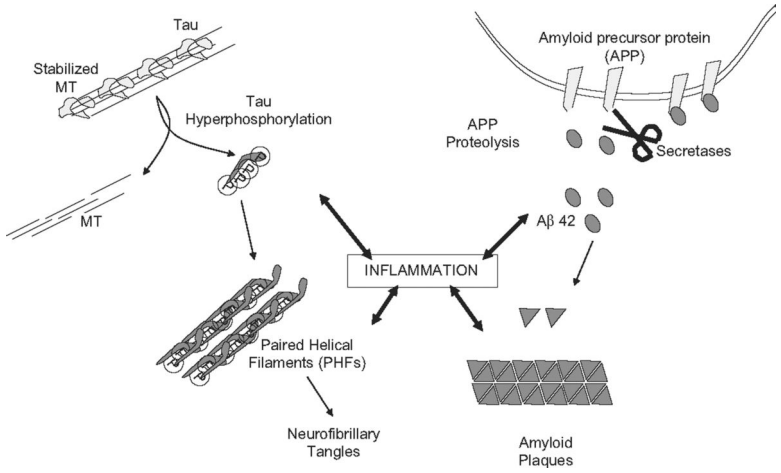

Fig. 1.

Characteristic pathological mechanisms and hallmarks found in AD patients. The typical pathological hallmarks of AD include the neurofibrillary tangles and amyloid plaques that represent the two characteristic biochemical processes of the disease: hyperphosphorylation of tau and misfolding of amyloid beta. Hyperphosphorylation of tau in AD patients favors its dissociation from the microtubules and its accumulation in paired helical filaments (PHFs). PHFs aggregate into detrimental clusters inside nerve cell bodies known as *neurofibrillary tangles* and as dystrophic neurites associated with amyloid plaques. The massive dissociation of tau from microtubules also interferes with the axonal transport and contributes to the loss of synapses and neuronal degeneration correlated with the cognitive impairments of the AD patients. AD is also associated with the accumulation of abnormal folded amyloid beta$_{1–42}$ (Aβ42) in the amyloid plaques. More comprehensive strategies are currently directed to determine the etiology of AD and the potential contribution of inflammation to both the pathogenesis and prognosis of AD.

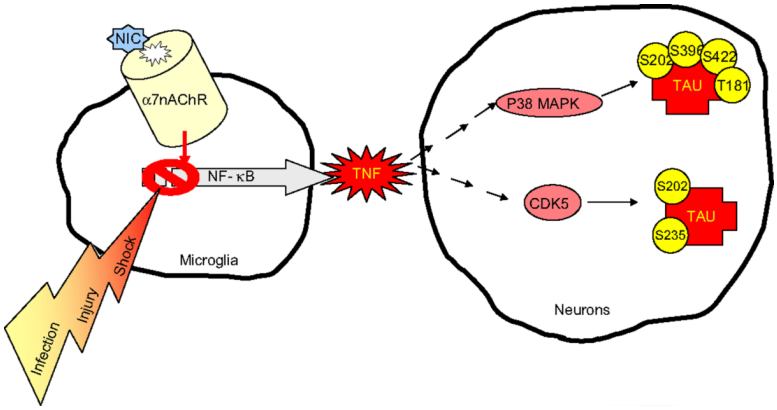

Fig. 2.

Effect of nicotine-alpha7nAChRs interaction on tau phosphorylation. The nicotine-alpha7nAChRs interaction inhibits the production of TNF in LPS-stimulated mouse microglial cultures through inhibition of the NF-κB pathway. This inhibition of TNF is associated with a reduction in phosphorylation of ERK and p38 MAPK. P38 MAPK can phosphorylates tau in neurons and glia. A reduction of p38 MAPK may prevent tau phosphorylation at S202, S296, S422 and T181. Activated microglia colocalize with amyloid plaques and facilitate amyloid clearance but can also phosphorylate tau through release of proinflammatory cytokines (including TNF), chemokines and other inflammatory components. Activation of the cdk5/p25 complex has also been proposed as underlying mechanism in the phosphorylation of tau at S202 and S235.

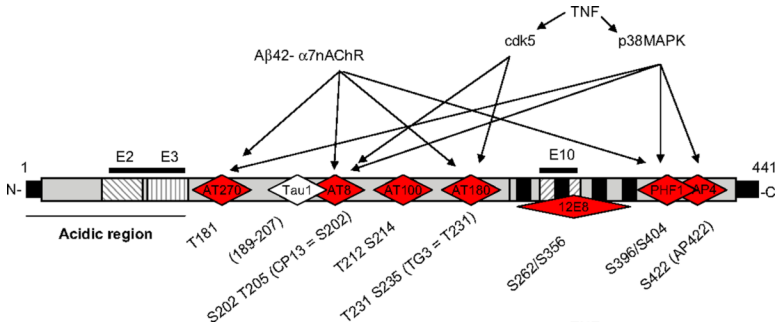

Fig. 3.

Schematic diagram showing the phospho tau epitopes affected by the Abeta42-alpha7nAChR interaction and the kinases activated by TNF in the longest isoform of tau. Tau isoforms are generated by splicing in or out exons 2, 3 and 10 (E2, E3 and E10). Red rhomboids are the different antibodies at specific phospho-tau epitopes. Abeta42 can phosphorylate tau at specific sites (T181, S202, T231 and S396/404) and TNF can activate kinases cdk5 and p38MAPK that phosphorylate tau at S202 and S235 (cdk5) and T181, S202, S396 and S422 (p30MAPK).

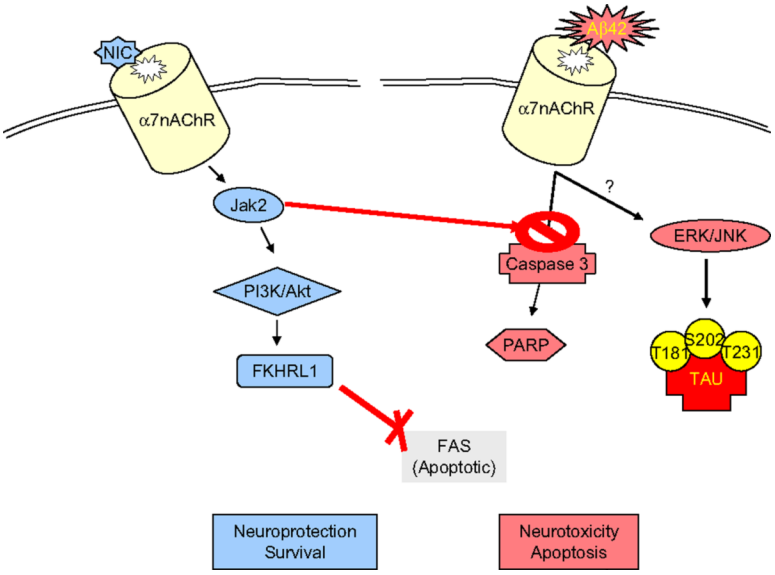

Fig. 4.

Schematic of the nicotinic-alpha7nAChR mediated activation of Jak2 neuroprotective pathway. The Abeta42-alpha7nAChR interaction activates the apoptotic enzyme caspase 3 and produces cleavage of the DNA-repairing enzyme poly-(ADP-ribose) polymerase causing eventually neurotoxicity and cell death. This cascade is inhibited by nicotinic activation of the JAK2-PI3K-Akt signaling pathway, promoting neuroprotection and cell survival. Activation of the anti-apoptotic kinase Akt involves phosphorylation of the forkhead transcription factor (FKHRL1), blocking eventually the expression of the apoptotic FAS protein. The Abeta42-alpha7nAChR interaction also produces increases in intracellular Ca^{2+} with activation of mitogen-activated kinase proteins ERK and JNK inducing tau hyperphosphorylation.