[Frontiers in Bioscience 12, 5030-5038, September 1, 2007]

Beta-amyloid peptide – nicotinic acetylcholine receptor interaction: the two faces of health and disease

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1. ABSTRACT

Elevated amyloid-beta peptide (Abeta) and loss of nicotinic acetylcholine receptors (nAChRs) stand prominently in the etiology of Alzheimer's disease (AD). Since the discovery of an Abeta - nAChR interaction, much effort has been expended to understand how this interaction may contribute to normal physiological processes as well as AD. Several researchers have expanded on the initial observation of an Abeta-nAChR interaction to characterize the pertinent factors that confer Abeta sensitivity to nAChRs. Some of which include the following: 1. receptor subunit composition; 2. receptor subunit stoichiometry; 3. regional distribution; 4. presynaptic versus somatic distribution; 5. neuron versus glia expression; 6. *in vitro* expression system. These aspects of nAChR composition and expression appear to confer the specific functional consequences of Abeta interaction which range from blockade of receptor activation to stimulation of second messenger cascades that provide neuroprotection from Abeta toxicity. This review will discuss the extant literature on the subject in terms of clarifying this apparent dichotomy regarding the consequences of Abeta – nAChR interaction during health and disease.

2. INTRODUCTION

The hippocampus and neocortex are early targets of accumulating beta-amyloid peptide (Abeta) in Alzheimer's disease (AD) that manifests itself as episodic memory impairment. Episodic memory deficits result from compromised cholinergic neurotransmission (1-4). The major source of cholinergic input to the hippocampus and neocortex is from the basal forebrain, including the medial septal nucleus, diagonal band nuclei, and nucleus basalis. The cholinergic deficit in AD is due in part to a depletion of nicotinic acetylcholine receptors (nAChRs) on these cholinergic projection neurons as well as on neurons within cortical areas (5-8). nAChRs flux the pluripotent second messenger Ca^{2+} and have been shown to modulate neuron excitability, the induction of LTP, and mediate the cognitive enhancing effects of *in vivo* administered nicotine (9-13). Nicotine treatment has been shown to improve attention, as well as learning and memory performance in patients with mild to moderate AD, as do drugs that potentiate central cholinergic function (14-18). Thus, nAChRs, either on cholinergic projection neurons or within the cortex are important for the types of cognitive performance that are impaired in early AD.

The recent discovery of a high affinity interaction between Abeta and nAChRs has opened up new avenues of investigation into how Abeţa- nAChR interaction may influence the physiology of nAChR-expressing cells (19, 20). At the forefront of this effort is to reconcile how this interaction likely serves both a normal physiologic role as well as contributing to the molecular etiology of AD. Current knowledge indicates that under non-disease conditions, Abeta – nAChR interaction may play a role in synaptic plasticity and homeostasis whereas under disease conditions, Abeta – nAChR interaction may contribute significantly to the molecular etiology of the disease. This review will discuss the extant literature on the subject in terms of clarifying this apparent dichotomy regarding the consequences of Abeta – nAChR interaction during health and disease.

3. EVIDENCE FOR ABETA – NACHR INTERACTION

There are several examples in the literature reporting that neuronal nAChRs as well as the muscle nAChR interact with $Abeta_{1-40}$ and $Abeta_{1-42}$ (19-32). Initial work published by Wang *et al* (19, 20) demonstrated that alpha7 nAChRs and Abeta are co-localized in AD cortical regions including the hippocampus; these proteins are found not only in the membrane fraction but also in amyloid plaque deposits. The receptor – peptide complex can be co-immunoprecipitated and detected with immunoblot; this was demonstrated for both control and AD brain samples. Because this association resists detergent treatment, it suggests that alpha7 nAChRs and Abeta may associate for extended periods and possibly serve as a point of nucleation for plaque formation (25). Competition binding studies on membrane preparations from brain regions and cell lines expressing the alpha7 nAChR indicated that Abeta association occurred with an affinity in the low picomolar range while similar experiments for alpha4beta2 nAChRs indicated an affinity 100 – 5,000 times lower (19, 20). The apparent affinity for alpha7 nAChR – $Abeta_{1-42}$ interaction and the fact that $Abeta_{1-42}$ in healthy brain has been estimated in the low pM range indicates that these two proteins could associate under normal physiologic conditions. Curve fit analysis suggested that there were two saturable Abeta binding sites on the alpha7 and alpha4beta2 nAChRs. *In vitro* work by Nagele *et al.*(19, 20, 25) indicates that alpha7 nAChR association with Abeta leads to internalization of the peptide – receptor complex providing a potential mechanism for intracellular Abeta accumulation and toxicity. In addition, prolonged *in vitro* exposure to Abeta led to cell toxicity in cells that expressed alpha7 nAChRs; this was blocked by alpha7 nAChR antagonists and was absent in preparations devoid of alpha7 nAChRs (20, 25). Thus, Abeta – alpha7 nAChR interaction may be a mechanism by which amyloid accumulates and deposits in the CNS, in addition, it may be a mediator of Abeta toxicity. However, it must be stated that there is also ample evidence that nAChRs *protect* against Abeta toxicity under certain conditions of high Abeta concentration and that low concentrations of soluble $Abeta_{1-42}$ actually lead to the transient stimulation of neuroprotective pathways via alpha7 AChRs (22).

3.1. Abeţa- nAChR interaction leads to receptor activation and inhibition

There is evidence in the literature for both an inhibitory effect as well as the ability of Abeta to activate nAChRs. On the surface these reports appear contradictory; however the biological preparations and methods of detection vary amongst laboratories. These differences indicate that the cell population, subcellular location, subunit stoichiometry, accessory proteins, and post-translational modifications may significantly influence the net effect of Abeta on nAChRs. An additional variable is the way in which the Abeta peptide stock solutions were prepared and handled. It is becoming quite clear that the tertiary structure and aggregation state of Abeta confers unique functional properties including the ability to perturb synaptic transmission and negatively influence learning and memory. For example, several lines of evidence support the notion that early cognitive deficits in AD mouse models are triggered by oligomeric assemblies of Abeta rather than plaque-associated Abeta (33, 34) . Recently, it has been demonstrated that purified oligomers (dimers and trimers as well as a 56 kDa dodecamer aggregate) of *in vitro* and *in vivo* produced Abeta can disrupt cognitive function (33, 34).

The work reviewed here exclusively used freshly prepared, soluble Abeta however the precise structure and aggregation state of the peptide is unknown in these studies. We attempted to evaluate the aggregation state of our freshly prepared human and rat $Abeta_{1-42}$. We found that these preparations predominantly contained monomer, trimer and hexamer oligomers based on molecular weight estimates, yet it is completely unknown which subset (or all) of these structures are responsible for our reported findings (21, 35, 36). Presumably, future work will correlate the effects of Abeta – nAChR interaction with specific peptide structures.

The first indication that $Abeta_{1-42}$ and nAChRs functionally interact was reported by Yakel's group in which they demonstrated that $Abeta_{1-42}$ inhibited nAChR currents recorded from GABAergic neurons in acutely prepared hippocampal slices (27). Caged-carbachol-induced currents measured with whole cell recordings were maximally inhibited 39% with a dose of 500 nM peptide. Doses as low as 100 nM were effective. These effects were rapidly reversible under whole-cell recording conditions. Patch clamp experiments revealed that $Abeta_{1-42}$ decreased open channel probability of two channel conductances: 38 pS conductance was maximally inhibited 15%; 62 pS conductance was maximally inhibited 55%. The 38 pS channel was sensitive to the alpha7-selective antagonist methyllycaconitine (MLA) indicating that non-alpha7 nAChRs (alpha4beta2?) were more sensitive to Abeta inhibition than alpha7 nAChRs. The outside-out configuration used in the patch clamp studies support the notion that $Abeta_{1-42}$ interacts directly with the extracellular portion of the receptors. This study demonstrated that GABAergic interneurons express nAChRs that are differentially sensitive to $Abeta_{1-42}$ inhibition; non-alpha7 nAChRs are more sensitive to inhibition and inhibition is reversible.

Subsequent work from this same group studied $Abeta_{1-42}$ effects on nAChRs expressed in *Xenopus* oocytes (28). Co-application of a maximal dose of carbachol and 1 μM $Abeta_{1-42}$ to oocytes expressing either alpha4beta2, alpha2beta2, alpha4alpha5beta2, or alpha7 nAChRs resulted in $Abeta_{1-42}$ inhibition of all receptor currents except those generated by alpha7 nAChR activation. The lack of an effect on alpha7 nAChRs expressed by *Xenopus* oocytes contrasts with their previous findings in hippocampal interneurons; further suggesting that the *in situ* environment significantly contributes to this receptor property. For the non-alpha7 nAChRs, the relative block by Abeta was dependent on the subunit makeup and stoichiometry of the expressed receptors. For example, alpha2beta2 nAChRs were equally susceptible as alpha4beta2 nAChRs to $Abeta_{1-42}$ inhibition (~18% inhibition under conditions of maximal carbachol activation) and inclusion of alpha5 in the alpha4beta2 receptor complex resulted in a decrease in Abeta inhibition of whole cell currents. Furthermore, shifting the ratio of injected alpha4:beta2 RNA from 1:1 to 3:1 also decreased the expressed receptor's susceptibility to Abeta inhibition. These studies clearly establish that subunit stoichiometry and nAChR subunit composition confer sensitivity to $Abeta_{1-42}$ inhibition.

Somewhat different results were obtained by Liu *et al.* (32) in which it was demonstrated that the response of both somato-dendritic and presynaptic hippocampal alpha7 nAChRs was almost completely blocked by exposure to $Abeta_{1-42}$ and non-alpha7 nAChRs expressed by the neurons were insensitive. This study used cultured hippocampal neurons and demonstrated that maximal $Abeta_{1-42}$ inhibition approached 80% and occurred within 1 min of peptide exposure. Full recovery occurred within 5 min of washout. These studies yielded an IC_{50} of 7.5 nM. The inhibition was noncompetitive as demonstrated with competitive binding assays using [^{125}I]-BTX. Blockade was voltage-independent and did not appear to result from Abeta acting as an open channel blocker, because prior receptor activation was not required for inhibition. Inhibition was most likely exerted through the N-terminal extracellular portion of the receptor since a functional chimera receptor comprised of the N-terminal extracellular domain of alpha7 nAChR subunit and the transmembrane and cytoplasmic domains of the related $5HT_3$ subunit was still sensitive but the intact $5HT_3$ receptor was not. Furthermore, it was determined that intracellular Ca^{2+} and G-protein activity was not necessary for inhibition of alpha7 nAChR function by $Abeta_{1-42}$.

Related to the above work by Petit *et al.* (27)and Liu *et al.* (32), Wu *et al.*(30) tested the effects of $Abeta_{1-42}$ on human alpha4beta2 nAChRs stably expressed by human SH-EP1 cells. It was found that $Abeta_{1-42}$, at doses as low as 1 nM, led to about 25% reduction of peak and steady-state currents elicited from these receptors with either nicotine or acetylcholine. Peak responses were inhibited by $Abeta_{1-42}$ in a dose-dependent manner. Investigations into the possible mechanisms determined that, similar to the findings of Liu *et al.* (32) with alpha7 nAChRs expressed on cultured hippocampal neurons, inhibition is non-competitive, voltage-independent, does not require receptor pre-activation, is not dependent on G-protein activation, and does not require the intracellular or transmembrane domains of the alpha subunit. All the above studies found that pre-application of the peptide is required in order to achieve receptor inhibition and receptor inhibition is reversible (27, 28, 30, 32).

Instead of receptor antagonism, Pym *et al.* (26) found that Abeta peptides enhanced acetylcholine activation of human alpha4beta2 nAChRs expressed in *Xenopus* oocytes. 10 nM $Abeta_{1-42}$ and $Abeta_{1-40}$ increase the maximum acetylcholine current by almost 100%. A stoichiometry effect was also measured; the greatest effect for Abeta potentiation of receptor function occurred when the alpha beta ratio was greater than one. Consistent with the findings of Lamb *et al.* (28), the work described by Pym *et al.* (26) also found that human alpha7 nAChR were antagonized by $Abeta_{1-42}$ (and $Abeta_{1-40}$). Maximum acetylcholine currents were inhibited approximately 50% in the presence of 10 nM of either peptide. Concentrations in the range of 1 pM – 100 nM were tested and failed to activate the receptor. Similar to the above described studies, Pym *et al.* (26) found that Abeta effects were reversible. Tests on alpha3beta4 nAChRs had no effect, again suggesting that subunit composition as well as receptor stoichiometry are important factors in sensitivity to modulation by Abeta.

Grassi *et al.* (24) also reported that human alpha7 nAChRs expressed in Xenopus oocytes were antagonized by 100 nM $Abeta_{1-42}$. Antagonism was non-competitive and an analysis of a dose response study for inhibition of currents elicited by 100 μM ACh yielded an IC_{50} of 90 nM. Attempts to activate these receptors with 10 nM $Abeta_{1-42}$ were unsuccessful.

Utilizing confocal imaging of isolated presynaptic nerve endings purified from rat hippocampus and neocortex, Nichols and colleagues (23) found that pM $Abeta_{1-42}$ directly led to sustained increases in presynaptic Ca^{2+} via nAChRs. The effect of $Abeta_{1-42}$ was sensitive to alpha-bungarotoxin (BTX), mecamylamine (MEC), and dihydro-beta-erythroidine (DHbetaE), indicating the involvement of both alpha7-containing and non-alpha7-containing nAChRs. Interestingly, it was discovered that alpha7-containing nAChRs are largely involved in the presynaptic actions of Abeta at pM concentrations whereas higher nM concentration of Abeta involves mainly non-alpha7-containing nAChRs. Prior exposure of these preparations to Abeta occluded subsequent nicotine-evoked increases in presynaptic Ca^{2+}. This and the fact that nicotine, albeit at relatively high concentration, could overcome the occlusion effect of Abeta suggested that the Abeta and the alpha7 nAChR ligand binding site significantly overlap.

Another demonstration that non-alpha7 nAChRs can be activated by Abeta was provided by Fu and Jhamandas (31) in which they found that neurons acutely isolated from the diagonal band nucleus of the basal forebrain cholinergic region were responsive to $Abeta_{1-42}$.

Cell attached patch recordings detected two single-channel conductances of 31 and 76 pS that were sensitive to 100 nM $Abeta_{1-42}$. The 76 pS channel was blocked by the broad spectrum nAChR antagonist, MEC, but not the alpha7 nAChR-selective antagonist MLA. Whole cell recordings confirmed these observations and further pharmacological characterization suggested that the 76 pS channel is an alpha4-containing nAChR. The 31 pS conductance was insensitive to both MEC and MLA, leaving its identity unclear at this time. These studies indicate that on basal forebrain cholinergic neurons there is a population of non-alpha7 nAChRs that are activated by nM concentrations of $Abeta_{1-42}$.

We observed that rat alpha7 nAChRs expressed in *Xenopus laevis* oocytes were activated following application of femtomolar (fM) to nM concentrations of Abeta (36) . Receptor activation led to Ca^{2+} influx as evidenced by a reduction in current amplitude when Ca^{2+} in the recording solution was replaced by Ba^{2+}, thus preventing the activation of the endogenous Ca^{2+}-activated chloride current that enhances membrane depolarization. $Abeta_{1-42}$ activation of alpha7 nAChRs was blocked by alpha7-selective antagonist MLA and cross-desensitized by the alpha7-selective agonist 4-OH-GTS-21, suggesting that the alpha7 nAChR ligand binding domain and the $Abeta_{1-42}$ binding site at least partially overlap. $Abeta_{1-42}$ was more potent in activating alpha7 nAChRs than $Abeta_{1-40}$, consistent with the binding studies performed by Wang *et al.* (19) in which it was observed that alpha7 nAChRs exhibit higher affinity for $Abeta_{1-42}$ versus $Abeta_{1-40}$. While we demonstrated that Abeta peptides could directly activate alpha7 nAChRs; high doses or prolonged exposure to $Abeta_{1-42}$ led to receptor inhibition, possibly through a desensitization mechanism. This was suggested by the inverted U shape of the dose – response curve and the observation that more than one exposure or pre-exposure to $Abeta_{1-42}$ led to alpha7 nAChR inactivation. All in all, these studies put forth the possibility that, under normal physiologic conditions, Abeta and alpha7 nAChRs interaction could possibly lead to receptor activation. The presently known downstream consequences of such an interaction will be discussed in the following section.

Whether or not Abeta activates nAChRs *in vivo* is still controversial; however, it seems clear from these several studies using a variety of preparations that prolonged exposure to a moderate concentration of soluble Abeta leads to nAChR antagonism.

3.2. intracellular consequences of Abeta – nAChR interaction

3.2.1. non-alpha7 nAChRs

Other than the several reports for receptor antagonism, little is known about the downstream events following Abeta interaction with non-alpha7nAChRs. As is the case for receptor activation by ACh or nicotine, Abeta activation of non-alpha7 nAChRs leads to membrane depolarization (23, 31). In addition, the study by Dougherty *et al.* (23) demonstrated that this receptor type contributes to the Abeta-evoked increase in presynaptic Ca^{2+}, possibly contributing to neurotransmitter release. It will be of interest to investigate the commonalities and differences of somatic versus synaptic non-alpha7 nAChR activation as well as if there are inherent differences in receptor properties based on regional brain localization.

3.2.2. alpha7-containing nAChRs

Since the discovery of an alpha7 – Abeta interaction we and others have mapped out some of the downstream consequences of this association including calcium influx, ERK MAPK activation via the PI3K pathway that results in CREB phosphorylation in both a PKA- and Rsk2-dependent manner(21, 23, 35, 36) . The studies by Dineley *et al* (21) and Bell *et al.* (35)were performed on organotypic hippocampal slice cultures; specificity of the effects occurring via alpha7 nAChRs was demonstrated with the alpha7-selective antagonists MLA and BTX. ERK activation occurred rapidly and at concentrations as low as 10 pM.

Extended exposure to high (nM) concentration of $Abeta_{1-42}$ led to down-regulation of ERK MAPK activity; this is also observed in hippocampal samples from aged Tg2576 in which Abeta is produced in excess from young adulthood onward (21, 35). Interestingly, extended exposure to nM $Abeta_{1-42}$ up-regulates alpha7 nAChRs in hippocampal cultures, comparable to the effects of chronic exposure to nicotine (21). Likewise, in the Tg2576 hippocampus alpha7 nAChRs continue to up-regulate with age as Abeta accumulates, providing further evidence that Abeta and alpha7 nAChRs interact *in vitro* and *in vivo* (21, 37). Dysregulation of alpha7 nAChRs, ERK MAPK, and the downstream transcription factor CREB in the hippocampus of Tg2576 mice occurs concomitant with the onset of hippocampus-dependent learning and memory impairment(21). These combined *in vitro* findings and *in vivo* observations suggest that, in hippocampus, physiological concentrations of $Abeta_{1-42}$ impinge upon signal transduction cascades important for synaptic plasticity, learning and memory, and homeostasis. Short exposure times (minutes) and moderate concentrations (pM – low nM) do not lead to permanent changes in alpha7 or the ERK MAPK cascade; higher doses and extended exposure time lead to dysregulation of alpha7, ERK MAPK, and CREB accompanied by learning and memory impairments.

Work by Wang *et al.*(29) extended these findings to include tau phosphorylation resulting from both ERK MAPK and JNK-1 MAPK activation via 100 nM $Abeta_{1-42}$ and alpha7 nAChR interaction. There are three proline-directed MAPK-targeted serine (S) or threonine (T) residues on tau; 100 nM $Abeta_{1-42}$-evoked ERK MAPK activation led to phosphorylation of two (S202, T181) and $Abeta_{1-42}$-evoked JNK-1 MAPK activation led to phosphorylation of all three (S202, T231, T181). Residues S202 and T181 are known to modulate the kinetics of tau binding to microtubules which can eventually lead to microtubule instability (38). Utilizing cell lines and human brain synaptosomes, Abeta-induced tau phosphorylation was blocked by the alpha7-selective antagonists MLA and BTX as well as antisense knockdown of alpha7 protein in cultured neuroblastoma cells. These data open up the

possibility that a significant part of the etiology of AD, tau hyperphosphorylation and ensuing neurofibrillary tangle formation, might be mediated, at least in part, through nAChR – Abeta interaction. In support of this, Oddo *et al.* (39) recently reported that chronic nicotine treatment exacerbated tau pathology in a transgenic animal model in which mutant human transgenes for tau, APP, and PS-1 are expressed (40-42). Although the exact subtype of nAChR that mediates this effect was not directly tested, nicotine treatment led to a selective up-regulation of alpha4beta2 nAChRs, as measured with epibatidine binding. While alpha7 nAChRs are present in the triple transgenic animal, this mouse model exhibits age-dependent loss of alpha7 nAChR BTX binding in several brain regions and nicotine treatment had no effect on this parameter. Nicotine treatment corresponded with an increase in p38 MAPK activity but not other putative tau kinases, including GSK3beta, ERK MAPK, and CDK5. While it is unclear if alpha7 nAChRs are involved in the nicotine-induced alterations in tau phosphorylation and p38 MAPK activity in this mouse model; these data provide evidence that nAChR modulation under conditions of excess Abetą and possibly directly through Abeta – nAChR interaction, may contribute to tau pathology in AD.

Clearly these observations imply that the relationship between nAChRs and Abeta is a dynamic one and relies on several factors such as the *in situ* environment in which the nAChR is expressed (somatic, dendritic, presynaptic; neuronal, astrocytic, microglial) as well as the *in situ* status of Abeta (concentration, aggregation state, regional distribution).

4. ROLE OF ABETA – NACHR INTERACTION IN HEALTH AND DISEASE

4.1. nAChRs protect against Abeta toxicity

The evidence that nicotinic receptors perform a neuroprotective role in AD has a long and enigmatic history. Some epidemiological studies have concluded that smoking is negatively correlated with AD incidence (43) ; the fact that nAChRs on cholinergic projection neurons are severely depleted in early stages of the disease indicates that these receptors are an important component of the pathophysiology of AD (44, 45). While several studies have demonstrated that nAChR activation attenuates Abeta toxicity it is unclear why these receptors are selectively depleted in the disease. Specifically pertaining to protection against Abeta toxicity, *in vitro* studies utilizing cultured neurons have demonstrated that both alpha4beta2 and alpha7 nAChRs mediate the neuroprotective effects of nicotine (46). Protection against Abeta toxicity is proportional to the number of alpha7 nAChRs expressed by cultured cells (47). Chronic exposure to $Abeta_{1-42}$ *in vitro* leads to up-regulation of alpha7 nAChRs in a manner similar to the effects of chronic nicotine treatment (21, 37). Tg2576 mice that produce excessive Abetą continue to up-regulate alpha7 nAChRs as these animals age, possibly providing an explanation as to why this AD model does not exhibit significant neuronal loss (21, 37).

nAChR-mediated neuroprotection against Abeta is via activation of the PI3K pathway; several lines of evidence suggest that this can occur through transactivation of src and tyrosine kinase receptors, including the high-affinity NGF receptor, TrkA (47-50) . Paradoxically, at low to moderate concentrations of soluble $Abeta_{1-42,}$ PI3K is also activated, suggesting that when Abeta is soluble and at non-disease concentration, Abeta - nAChR interaction can lead to activation of neurotrophic mechanisms. *In vitro* and *in vivo*, chronic nicotine leads to an increase in TrkA, in addition to alpha7 and alpha4beta2 nAChRs; *in vivo*, this is accompanied by up-regulation of ChAT and VAChT in hippocampus (51, 52) . Increased TrkA is neuroprotective against Abeta toxicity; high concentrations of Abeta are neurotoxic and block nicotine-induced TrkA upregulation (50, 52). Thus, nAChRs are neuroprotective both by modulating the neurotrophic system crucial for the maintenance of cholinergic neuron integrity as well as stimulating signal transduction pathways that support neuron survival. Additionally, these studies suggest that in a situation of excess Abetą nAChR function, and hence, trophic activity is blocked; possibly contributing to Abeta toxicity. Taken together, one might imagine that under normal physiologic conditions, Abeta – nAChR interaction provides a trophic signal; as Abeta accumulates, this interaction either blocks nAChR-mediated trophism or Abeta – nAChR interaction under these circumstances becomes toxic.

4.2. Abetą– nAChR interaction under normal physiological conditions

It is noteworthy that estimates of Abeta content in non-demented brain report pM values whereas in AD these estimates increase to nM quantities (41, 42, 53, 54). Based on these estimates and the binding studies of Wang *et al.* (19, 20), it is plausible that under normal physiologic conditions Abeta is present at a sufficient concentration for interaction with nAChRs. Studies on the biological consequences of an Abeta – nAChR interaction under 'low Abeta' conditions support the notion that this leads to the transient activation of second messenger systems that serve a neuroprotective role, such as the ERK MAPK and PI3K cascades (21, 35, 55; also, see below). Therefore, under normal physiologic conditions, Abeta – nAChR interaction may impinge upon signal transduction mechanisms important for synaptic plasticity and neuron homeostasis.

Several studies report that prolonged exposure of nAChRs to nM Abeta results in significant block of receptor function (24, 26-28, 32, 36). This suggests that under disease conditions Abeta – nAChR interaction would interfere with the normal function of these receptors. Given the overwhelming evidence that nAChRs perform a neuroprotective role, Abeta – nAChR interaction under elevated Abeta conditions may exacerbate the toxicity of Abeta by diminishing the neuroprotective signaling performed by these receptors. The current literature indicates that additional outcomes of an Abeta – nAChR interaction under 'high Abeta' conditions could yield 1) perturbation and dysregulation of signal transduction mechanisms involved in synaptic plasticity and homeostasis; 2) receptor – peptide complex internalization; 3) cell toxicity; and 4) plaque seeding. The evidence for these mechanisms will be discussed in the following section.

4.3. Abeta, nAChRs, and Alzheimer's disease

The hippocampus and cortex are early targets of accumulating Abeta in AD that manifest as episodic memory impairment. Episodic memory deficits result from compromised cholinergic neurotransmission (1-4). The cholinergic deficit in AD is due to a depletion of alpha7- and alpha4- containing nAChRs on cholinergic projection neurons as well as on neurons within cortical regions including the hippocampus (5-8). As discussed above, nAChRs flux the pluripotent second messenger Ca^{2+} and have been shown to modulate hippocampal pyramidal neuron excitability, the induction of LTP, and mediate the cognitive enhancing effects of *in vivo* administered nicotine(9-13). Nicotine treatment has been shown to improve attention, as well as hippocampus-dependent learning and memory performance in patients with mild to moderate AD, as do drugs that potentiate central cholinergic function (14-18) . Thus, nAChRs, either on cholinergic projection neurons to or within cortical regions are important for the types of cognitive performance that are impaired in early AD. Understanding the molecular mechanism underlying the selective vulnerability of cholinergic neurons to Abeta toxicity would greatly advance our capabilities in treating AD. The fact that vulnerable neuron populations happen to be enriched for nAChRs may provide an important clue. As discussed previously, one possibility as Abeta accumulates during AD, is that the neuroprotective function of nAChR activation is blocked by the antagonizing effect of Abeta peptides. Another possibility is that Abeta – nAChR interaction under disease conditions directly contributes to neurotoxicity. Recent work by Nagale and colleagues provide support for this mechanism.

While there is a general consensus that the presence of excess Abeta is perhaps the most fundamental neurotoxic event in AD, several lines of evidence indicate that oligomeric, soluble forms of Abeta, rather than amyloid plaques, initiate the cognitive deficits characteristic of the disease (56, 57). For example, transgenic mouse models for AD, in which Abeta is over produced and accumulates in the CNS, develop memory impairments long before plaques are detected and in the absence of significant neuronal loss (37, 58-60). Furthermore, introduction of Abeta oligomers produced *in vitro* or *in vivo* induces learning and memory deficits in wildtype rodents that resemble those of transgenic models for AD (33, 34). Therefore, some of the cognitive impairments in AD may not be associated with extensive neuronal death; rather, they may be the result of more subtle functional changes induced by soluble Abeta. It will be important for future studies of Abeta – nAChR interaction to attribute outcomes of this interaction not only to the concentration of soluble Abeta but also to specific structures and aggregates of the peptide.

More recently, emerging evidence indicates that intracellular Abeta may play a critical role in the disease process as well. In a series of publications from Wang, Nagale, D'Andrea and colleagues, it has been reported that $Abeta_{1-42}$ accumulates intracellularly in neurons of AD brains, and neurons that had accumulated large amounts of $Abeta_{1-42}$ also highly expressed the alpha7 nAChR (25, 61). In neuroblastoma cells transfected with alpha7 nAChR cDNA, transfected cells exhibited rapid binding, internalization and accumulation of exogenous $Abeta_{1-42}$, but not $Abeta_{1-40}$; this internalization was related to the level of alpha7 nAChR expression. Further, the alpha7 nAChR antagonist, BTX, prevented $Abeta_{1-42}$ uptake. These results suggest that alpha7 nAChRs facilitate $Abeta_{1-42}$ internalization in neurons and may confer selective vulnerability to the toxic effects of intracellular $Abeta_{1-42}$ (25).

Nagale (62, 63) and colleagues took this notion a step further by suggesting that nAChR – Abeta interaction and internalization may actually lead to plaque formation when the host cell eventually dies and deposits the intracellular contents in the brain parenchyma. Nagale's work also provided the first indication that nAChR – Abeta interaction in astrocytes may be an important event in the inflammatory progression of the disease. These studies described that $Abeta_{1-42}$ and alpha7 nAChR were co-localized in intensely GFAP-positive (activated) astrocytes in immunostained AD brain. Since these studies also identified choline acetyltransferase (ChAT), the authors proposed a model in which Abeta and alpha7 proteins are phagocytosed by activated astrocytes in the vicinity of neuronal remnants. As neuronal debris accumulates in the astrocyte, astrocyte viability is compromised and eventually kills the cell leaving behind Abeta deposits rich in astrocytic GFAP, and neuronal markers such as ChAT and alpha7 protein.

A slightly different interpretation was made by Teaktong *et al.* (64) when they found that the majority of astrocytes in AD hippocampus and cortex also express alpha7 nAChRs; this group deduced that alpha7 nAChRs are up-regulated in the disease. Subsequent *in vitro* work by Xiu *et al.* (65) lends support to the idea that nAChR up-regulation on astrocytes occurs in the disease: exposure of cultured primary astrocytes to pM – nM $Abeta_{1-42}$ for 48 hours followed by quantification of mRNA and protein with RT-PCR and immunoblot, respectively, resulted in up-regulation of both alpha7 nAChR mRNA and protein. In addition, alpha4 and beta2 subunits were also up-regulated in treated cultures; beta3 nAChR subunit remained unchanged. While it has yet to be directly tested, possibly, nAChR – Abeta interaction on astrocytes leads to astrocyte activation and nAChR up-regulation; alternatively, nAChR – Abeta complexes are present on degenerating dendritic and synaptic surfaces leading to internalization by activated astrocytes where intra-astrocytic Abeta then exerts its toxic effects on these cells. These observations reveal a possible link between nAChRs and the inflammatory processes of AD. It will be important to decipher this apparently complex relationship between neurotoxicity, astrocyte activation and toxicity and the development of neuronal- and astrocyte-derived plaques in AD brain as it has implications that Abeta – nAChR interaction results in a broad array of outcomes during the progression of AD.

Finally, since it appears that muscle nAChRs and Abeta interact, there are as yet to be explored implications

for muscle function and peripheral amyloid disease (24). Unfortunately, other than this initial observation, little has been elucidated on this topic.

5. PERSPECTIVE: WHAT ARE THE THERAPEUTIC OPPORTUNITIES BASED ON ABETA– NACHR INTERACTION?

While our understanding of Abeta – nAChR interaction is too immature to emphatically decide these issues, one can at least ponder the array of therapeutic opportunities with our current knowledge base. Given the potential that trophic signals are generated under normal physiologic conditions, it seems that prophylatically blocking Abeta – nAChR interaction is probably not necessary or even a prudent idea. However, as Abeta levels become pathologic, it might be useful to develop ways in which to interrupt Abeta – nAChR interaction, especially if this interaction is involved in accumulating intracellular Abeta or signaling toxicity. As is being currently pursued, targeting Abeta directly with immunotherapy is one way. From the nAChR side of the equation, the development of a decoy nAChR-like binding site might prevent a potentially toxic Abeta – nAChRs interaction. Direct modulation of nAChR function is another strategy. However this requires a solid understanding of the functional relationship between the receptor and peptide as Abeta levels increase and accumulate with disease progression. Clearly, while great strides have been made in understanding Abeta – nAChR interaction in recent years, the complex nature of this relationship demands that much has yet to be understood before emphatically stating what the best nAChR strategy is for AD.

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Key Words: Nicotinic, Cholinergic, Amyloid, Alzheimer's Disease, Neuroprotection, Alpha7, Review

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