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β-Amyloid Peptide Activates Non-α7 Nicotinic Acetylcholine Receptors in Rat Basal Forebrain Neurons

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Fu, Wen and Jack H. Jhamandas. β-Amyloid peptide activates non-α7 nicotinic acetylcholine receptors in rat basal forebrain neurons. J Neurophysiol 90: 3130–3136, 2003. First published July 30, 2003; 10.1152/jn.00616.2003. Alzheimer’s disease (AD) is a progressive neurodegenerative condition characterized by profound deficits in memory and cognitive function. Neuropathological hallmarks of the disease include a loss of basal forebrain cholinergic neurons and the deposition of β-amyloid peptide (Aβ) in neuritic plaques. At a cellular level, considerable attention has focused on a study of Aβ interactions with the neuronal nicotinic acetylcholine receptor (nAChR) subtypes. In this study, using cell-attached and outside-out single channel recordings from acutely dissociated rat basal forebrain neurons, we report that Aβ and nicotine activate nAChRs with two distinct levels of single-channel conductance. Whole cell recordings from these neurons reveal Aβ and nicotine, in a concentration-dependent and reversible manner, evoke brisk depolarizing responses and an inward current. The effects of Aβ on both single channel and whole cell are blocked by the noncompetitive nAChR antagonist mecamylamine and competitive nAChR antagonist dihydro-beta-erythroidine, but not the specific α7-selective nAChR antagonist methyllycaconitine, indicating that Aβ activated non-α7 nAChRs on basal forebrain neurons. In addition, the non-α7 nAChR agonists UB-165, epibatidine, and cytisine, but not the selective α7 agonist AR-R17779, induced similar responses as Aβ and nicotine. Thus non-α7 nAChRs may also represent a novel target in mediating the effects of Aβ in AD.

INTRODUCTION

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder that is characterized by impairment of learning and memory (Cummings and Cole 2002). Neuropathological and neurochemical hallmarks of this disease include the presence of extracellular neuritic plaques composed of β-amyloid peptide (Aβ), neurofibrillary tangles composed of tau protein, and a loss of cholinergic neurons of the basal forebrain (Selkoe 1999; Yankner 1996). Aβ plays an important role in AD pathophysiological process (Hardy 1997; Selkoe 2002), and the total Aβ content in the brain correlates with cognitive decline (Naslund et al. 2000). Although the precise mechanisms for Aβ-induced toxicity are not firmly established, Aβ and other peptide fragments derived from APP influence cellular homeostasis and neuronal signaling through modulation of ion channel function (Fraser et al. 1997). Neuronal nicotinic acetylcholine receptors (nAChRs) are a family of ligand-gated ion channels with multiple subtypes and widely distributed in the human brain. The nAChRs are involved in a number of physiological and behavioral processes and AD patients demonstrate reduced numbers of nAChRs in brain regions that are critical to cognition and memory (Paterson and Nordberg 2000). In aging rats, the loss of nAChR α4 subunit expression occurs in the medial septum and diagonal band (Rogers et al. 1998). In postmortem studies on brains from AD patients, levels of α4β2 subtype of nAChRs have been reported to be significantly and selectively diminished in the cerebral cortex (Martin-Ruiz et al. 1999; Warman and Nordberg 1995).

Aβ1–42 binds to α7 and α4β2 subtypes of nAChRs with high affinity in the picomolar and nanomolar range, respectively (Wang et al. 2000a,b). Recently, several reports indicate that Aβ modulates α7 nAChRs in hippocampal neurons (Liu et al. 2001; Pettit et al. 2001), human α7 nAChRs expressed in Xenopus oocytes (Dineley et al. 2002; Grassi et al. 2003), and Torpedo α7 and α4β2 nAChRs expressed in Xenopus oocytes (Tozaki et al. 2002). However, there are conflicting data concerning the precise nature of Aβ interactions with the α7-nAChRs. For instance, Aβ1–42 has been shown to inhibit α7-nAChR functions in rat hippocampal neurons (Liu et al. 2001; Pettit et al. 2001), but Aβ activates α7-nAChRs expressed in Xenopus oocytes (Dineley et al. 2002). In contrast to Aβ-α7-nAChR interactions, there is considerably less data on Aβ effects on non-α7 subtypes of nAChRs. In hippocampal slices, Aβ1–42 inhibits carbachol-induced current that is composed of contributions from activation of non-α7 nAChRs (Pettit et al. 2001).

Interactions of amyloid peptides with cholinergic neurons are considered to be a basis for the modified basal forebrain cholinergic function observed in AD (reviewed in Auld et al. 2002). Nicotinic acetylcholine receptors, particularly those containing the α4 subunit, are abundantly located within the rat basal forebrain cholinergic system (Perry et al. 2002). We hypothesize that non-α7 nAChRs may be important targets for Aβ interaction with cholinergic neurons of the basal forebrain. In this study, we use a combination of single channel and whole cell patch-clamp recordings to provide evidence for Aβ interactions with non-α7 subtype of nAChRs on neurons of the rat DBB, a basal forebrain cholinergic nucleus.

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**METHODS**

**Dissociation procedures**

Details of the procedure for acute dissociation of neurons from the DBB are described in Jassar et al. (1999). Briefly, brains were quickly removed from decapitated male Sprague-Dawley rats (15–25 days postnatal) and placed in cold artificial cerebrospinal fluid (ACSF) that contained (in mM) 140 NaCl, 2.5 KCl, 1.5 CaCl₂, 1.2 MgCl₂, 10 HEPES, and 33 D-glucose (pH 7.4). Brain slices (350 μm thick) were cut on a vibratome, and the area containing the DBB was dissected out. Although most of the tissue contained the horizontal limb of the DBB, some slices may have also included the vertical limb of the DBB. Acutely dissociated neurons were prepared by enzymatic treatment of slice with trypsin (0.65 mg/ml) at 30°C, followed by mechanical trituration for dispersion of individual cells. Cells were then plated on poly-L-lysine (0.005% wt/vol)–coated cover slips and viewed under an inverted microscope (Zeiss Axiovert 35, Carl Zeiss). All solutions were kept oxygenated by continuous bubbling with pure oxygen.

**Electrophysiological recordings**

All single channel and whole cell patch-clamp recordings were performed at room temperature (20–22°C) using an Axopatch 200B amplifier (Axon Instruments, Union City, CA). Acutely dissociated DBB neurons were identified for recording by visual inspection. Most of the cells demonstrated neuron-like morphology (i.e., large cells with a conspicuous nucleus, nucleolus, and a few blunt processes that were truncated axon/dendrites). Patch electrodes (World Precision Instruments, Sarasota, FL; thin wall with filament, 1.5 mm diam) were flame polished to yield resistances of 3–6 MΩ. For single channel cell-attached recordings, patch pipette solution contained (in mM) 140 cesium methanesulfonate, 10 HEPES, and 10 d-glucose, pH 7.2, adjusted with CsOH. The pipette solution also included either 2 μM nicotine, 4 μM Aβ₂₅₋₃₅, 4 μM Aβ₁₋₄₂, or 0.1 μM Aβ₁₋₄₂ alone or in combination with either 0.2–0.8 μM methyllycaconitine (MLA) or 0.2–0.8 μM mecamylamine (MCA). For single channel outside-out patch-clamp recordings, pipette solution contained (in mM) 140 K-methanesulfate, 10 EGTA, 5 MgCl₂, 1 CaCl₂, 10 HEPES, 2.2 Na₂-ATP, and 0.3 Na-GTP (pH 7.2). Single channel currents were recorded using a low-pass filter at 5 kHz and were digitized at 10 kHz. The average amplitudes of single channel currents were measured using all-points histograms well fitted by Gaussian distributions. The channel open probability (Pₒ) was estimated from the event lists determined with the Fetchan program (Axon Instruments). The detection of events was determined by the “50% threshold” method. Whole cell patch-clamp recordings were obtained using pipette solution that contained (in mM) 140 K-methanesulfate, 10 EGTA, 5 MgCl₂, 1 CaCl₂, 10 HEPES, 2.2 Na₂-ATP, and 0.3 Na-GTP (pH 7.2). After whole cell configuration was established with voltage-clamp mode (holding potential, −60 mV), we waited ≥5 min for the cell to stabilize and started either voltage-clamp studies or switched to current-clamp recording mode. The current and membrane voltages were recorded using a low-pass filter at 5 kHz and were digitized at 10 kHz. All data were acquired and analyzed using pClamp8 software (Axon Instruments).

**Drugs and solutions**

All chemicals used in electrophysiological recording were purchased from Sigma (St. Louis, MO) except the following: Aβ₂₅₋₃₅, Aβ₁₋₄₂ (QCB Biosource International, Camarillo, CA), UB-165 fumarate (Tocris Cookson, Ellisville, MO), and AR-R17779 (generous gift from Dr. S. Kar, McGill University). Stock solutions of Aβ peptides were prepared by dissolving the peptides at 1 mM in deionized water and storing in aliquots at −70°C. On the day of the experiment, Aβ peptides were diluted in internal (for single channel recordings) or external (for whole cell recordings) perfusing solution just before the time of application. For whole cell voltage- and current-clamp and single channel outside-out patch-clamp recordings, drugs were applied via a focal applicator from a micromanipod tip placed under visual guidance within 100 μm of the cell being recorded from (DAD-VC Voltage Command Valve Control System, ALA Scientific Instrument, Westbury, NY). The cells were continuously perfused with ACSF at approximately 1 ml/min, and in most cases, the onset to response to the drug was within 10 s. Data are expressed as mean ± SE. ANOVA was used for comparisons; in those instances where significant (P < 0.05) main effects were noted, individual group differences were determined by Newman-Keuls test.

**RESULTS**

A total of 203 cells (n = 59 rats) with a neuron-like morphology were used for the patch-clamp study. Of these, 90 cells (n = 32 rats) were used for single channel recording (85 cell-attached patches and 5 outside-out patches) and 113 cells (n = 27 rats) were used for whole cell recordings (current- or voltage-clamp modes).

**Single channel studies**

CELL-ATTACHED SINGLE CHANNEL RECORDINGS. In cell-attached single channel patch-clamp recordings, application of Aβ₂₅₋₃₅ (4 μM, n = 15), Aβ₁₋₄₂ (100 nM, n = 5), or nicotine (2 μM, n = 29) induced two identifiable single-channel events with distinct current levels (Fig. 1A–C), whereas the inverse fragment Aβ₃₅₋₃₅ (n = 5) did not result in single channel openings (Fig. 1D). At a membrane potential of ~70 mV, these current levels were 3.4 and 7.8 pA, which corresponded to conductance levels of 31 ± 2 and 76 ± 3 pS, respectively. The 76-pS channel was observed in 88% of the patches. This higher conductance channel was seen in isolation in 44% of the patches and with the co-existing 31-pS channel conductance in the balance of 44% of the patches. The 31-pS channel was not observed in isolation in any of the patches. No single channel activity was observed in 12% of the patches. The single channel current-voltage (I-V) relationship of both channel types was linear in the −70- to +10-mV range (Fig. 1E). No single channel activities were observed in cell-attached single channel recording when only patch pipette solution was used without any agonist (n = 8).

Either Aβ₂₅₋₃₅ (4 μM in the pipette, Fig. 2A) or nicotine (2 μM, Fig. 2B) induced the opening of observable single channel currents with a conductance level of 76 pS. Inclusion of MCA (0.2–0.8 μM, n = 10) in the patch pipette, a noncompetitive antagonist for nAChRs with a greater sensitivity for the non-α7 nAChRs, reduced the open probability of the 76-pS channel induced by Aβ₂₅₋₃₅ (Fig. 2C). However, MLA (0.2–0.8 μM, n = 9), an α7 nAChR selective antagonist, did not cause a significant change in the open probability of this channel (Fig. 2D). In an identical manner, MCA (n = 6), but not MLA (n = 6), caused a reduction in open probability of the 76 pS induced by application of nicotine.

The mean channel opening probability (Pₒ) of the 76-pS channel induced by Aβ₂₅₋₃₅ was significantly reduced from 4.5 ± 0.6 to 0.8 ± 0.6% by concomitant inclusion of MCA (0.2–0.8 μM) in the pipette at the membrane potential of ~70 mV (P < 0.05, Fig. 2E). On the other hand, MLA (0.2–0.8 μM) did not affect the Pₒ of the 76-pS channel (4.5 ± 0.6% without MLA vs. 8.2 ± 1.0% with MLA). No difference in Pₒ...
of the 31-pS channel was observed after the inclusion of either MCA or MLA in the pipette solution (Fig. 2F). Similarly, the nicotine-induced opening of the 76 pS was sensitive to blockade by MCA, but not MLA, across the voltage range tested (Fig. 2G). The 31-pS channel opening evoked by nicotine was not affected by either MCA or MLA (Fig. 2H).

**Outside-out patch single channel recordings.** Due to possible desensitization of the α7 nAChRs by inclusion of the nicotine or Aβ in the pipette (under cell-attached conditions), we also investigated the action of these compounds on the nAChRs by performing outside-out patch-clamp recordings in DBB neurons. Spontaneous brief openings were observed in all five excised patches obtained from different neurons at voltage clamped at −50 mV. Application of nicotine (100 μM, Fig. 3A), UB-165 (100 μM, Fig. 3C), and Aβ1–42 (0.1 μM, Fig. 3E) significantly raised single channel open probability. Channel activity was completely abolished by the non-α7 nAChR antagonist dihydro-beta-erythroidine (DHβE; 0.1 μM; Fig. 3, B, D, and F).

**Whole cell patch-clamp studies**

**Whole cell current-clamp recordings.** The resting membrane potential was measured at −79.0 ± 0.8 mV (n = 7), consistent with that reported previously for DBB neurons (Easaw et al. 1997). Whole cell recordings under current-clamp mode revealed application of either Aβ25-35 (n = 62), Aβ1–42 (n = 5), or nicotine- (n = 73) evoked depolarization of the DBB neurons (Fig. 4, A–C). The depolarization for Aβ25-35 (1 nM), Aβ1–42 (1 nM), and nicotine (1 nM) were 14.7 ± 6.6, 11.2 ± 3.5, and 16.3 ± 7.2 mV, respectively. Aβ did not affect spike threshold (the membrane potentials at the time point when first spike evoked by agonists, nicotine, or Aβ) compared with nicotine. The depolarization was concentration-dependent (Fig. 4D). Aβ and nicotine responses were tested in the same cells with application of lowest concentration first and subsequent application of progressively higher doses. The EC50 for Aβ25-35 and nicotine is 0.34 and 14.13 μM, respectively. We next demonstrated that as with the nicotine- and Aβ25-35-induced activation of the large conductance single channel, depolarizing effects of nicotine and Aβ25-35 could be blocked by MCA (0.2–0.8 μM, n = 15) and DHβE (0.1 μM, n = 6), but not by MLA (0.2–0.8 μM, n = 12). Figure 5A shows a representative DBB neuron in which MCA (0.8 μM) blocked the depolarizing effects of Aβ25-35 (1 nM). The depolarizing effect of Aβ25-35 was also blocked by 0.1 μM DHβE (Fig. 5C). In contrast, MLA (0.8 μM) had no effect on the Aβ25-35 response (Fig. 5E). Similarly, MCA (Fig. 5B, n = 21) and DHβE (Fig. 5D, n = 7), but not MLA (Fig. 5F, n = 16), blocked the nicotine-evoked depolarization of DBB neurons.

We also evaluated specific nAChR agonists for their ability to activate DBB neurons. UB-165, epibatidine, and cytisine are all non-α7 nicotinic receptor agonists with a high binding affinity for the α4β2 subtype of nAChRs (Sharples et al. 2000; Whiteaker et al. 1998). Applications of each of the three agonists resulted in a reproducible and reversible depolarization of DBB neurons (For UB-165, 20 μM, n = 12 cells, depolarization = 18.3 ± 5.2 mV; epibatidine, 20 μM, n = 5, depolarization = 12.8 ± 5.0 mV; cytisine, 20 μM, n = 6 cells, depolarization = 10.4 ± 7.4 mV; Fig. 6, A–C). AR-R17779 (20 μM), an agonist that is selective for the α7-nAChR, did not depolarize any of the DBB neurons that were tested (n = 5 cells, Fig. 6D). However, all five cells that did not respond to the α7-nAChR agonist AR-R17779 were depolarized by applications of nicotine, Aβ25-35, and the non-α7 nAChR agonist UB-165 (Fig. 6E).

**Whole cell voltage-clamp recordings.** Under whole cell voltage-clamp condition (holding potential, −80 mV), Aβ1–42 (10 nM, n = 6; 100 nM, n = 5; Fig. 7), in a concentration-dependent manner, evoked an nAChR-sensitive current. The current evoked by 10 nM Aβ was 98 ± 21 pA, and for 100 nM Aβ was 146 ± 33 pA. DHβE (0.1 μM) blocked Aβ effects (Fig. 7). All cells tested were responsive to nicotine (Fig. 7), and the currents for 1 μM (n = 6) and 1 mM (n = 5) nicotine were 89 ± 22 and 189 ± 54 pA, respectively. The nicotine effect was also blocked by DHβE (0.1 μM, Fig. 7).
Dihydro-beta-erythroidine (DHβE) and nicotine evoke depolarization that occurs through a 76-pS channel that is blocked by the non-cholinergic (Jhamandas et al. 2001), the α4 nAChRs activated by Aβ in this study are located on acetylcholine-synthesizing neurons of the basal forebrain.

Recently, several conflicting reports have appeared describing a high affinity interaction between Aβ and α7 nAChRs (Liu et al. 2001; Pettit et al. 2001; Wang et al. 2000a). In hippocampal neurons, Aβ has been shown to block the re-

**DISCUSSION**

In this study, we provide the first direct evidence of a novel role for Aβ(25–35) and Aβ(1–42) as activators of a non-α7 subtype of nAChRs in rat basal forebrain neurons. Single channel recordings indicate that Aβ and nicotinic activation of nAChRs occurs through a 76-pS channel that is blocked by the non-competitive nAChR antagonist MCA and not by the α7-selective blocker MLA. These observations at the single channel level are confirmed by whole cell data that show that equimolar concentrations of Aβ and nicotine evoke depolarization that are blocked by MCA and competitive nAChR antagonist DHβE but not by MLA. Sub-micromolar concentrations of DHβE selectively block rat αβ2 and to a lesser degree α3 subtypes of nAChRs (Alkondon and Albuquerque 1993; Harvey et al. 1996). However, it is the α4 rather than the α3 subunit that is predominantly localized in the rat basal forebrain (Perry et al. 2002). Collectively, our data from pharmacological antagonism of the nicotinic and Aβ responses and the localization of the specific subtypes of nAChRs suggest that the α4 nAChR is the target of nicotine and Aβ actions in the DBB. Since we have previously shown by single-cell RT-PCR analysis that only Aβ responsive basal forebrain cells are cholinergic (Jhamandas et al. 2001), the α4 nAChRs activated by Aβ in this study are located on acetylcholine-synthesizing neurons of the basal forebrain.

![Figure 2](http://jn.physiology.org/)  **FIG. 2.** Mecamylamine (MCA), a noncompetitive nicotinic acetylcholine receptor (nAChR) antagonist blocks the 76-pS channel. Under cell-attached recording conditions, application of either Aβ(25–35) (4 μM, A) or nicotine (2 μM, B), by inclusion in the internal pipette solution, induced the 76-pS channel openings. Inclusion of MCA (0.2 μM) with Aβ(25–35) in the pipette solution significantly blocked the 76-pS nAChR (C). However, concomitant methyllycaconitine (MLA; 0.2 μM) inclusion in the pipette solution did not affect the 76-pS channel activity (D). The Aβ(25–35)-induced channel open probability (Po) of the 76-pS channel was significantly reduced with inclusion of MCA, but not MLA, in pipette solution (E), whereas the 31-pS channel was not affected by either MCA or MLA (F). Nicotine-induced channel open probability of the 76-pS channel was similarly affected by MCA and not MLA (G). The 31-pS channel was unresponsive to MCA and MLA (H). *Significance at P < 0.05.

![Figure 3](http://jn.physiology.org/)  **FIG. 3.** In an outside-out patch from acute dissociated DBB neurons, spontaneous brief openings were observed in voltage clamp at ~50 mV. Nicotine (100 μM, A), UB-165 (100 μM, C), and Aβ(1–42) (0.1 μM, E) significantly raised single channel open probability. Dihydro-beta-erythroidine (DHβE; 0.1 μM) completely abolished the nicotine (B), UB-165 (D), and Aβ effects (F).
The selective agonist AR-R17779 (20 nM) blocks the Aβ effects (top right) in DBB neurons. In the same neuron, nicotine (1 μM and 1 mM, bottom left and middle, respectively) also evokes an inward current that is also blocked by DHβE (bottom right; holding potential, −80 mV).

To our knowledge, our study is the first report describing the functional interactions of Aβ with the non-α7 nAChRs in rat basal forebrain neurons.

The data in our study are consistent with a high affinity interaction between Aβ and α4 nAChRs because even doses of Aβ in the picomolar and femtomolar range evoked a postsynaptic depolarization of DBB neurons. These concentrations are approximately three- to fivefold lower than binding assays in synaptic membranes that show Aβ binds to non-α7 nAChRs in the nanomolar range (Wang et al. 2000b). Although the binding data indicate an even higher affinity of Aβ for the α7 nAChRs (in the picomolar range), we did not observe any electrophysiological effects of nicotine or AR-R17779, an agonist selective for the α7 nAChRs, that could be attributed to a specific activation of α7 nAChRs. Nicotine applied under cell-attached conditions did infrequently activate a lower conductance 31-pS channel. Initially we considered the possibility that the 31-pS channel may be an α7 nAChR-sensitive conductance, based on the observation of similar single channel conductance of 38 pS in hippocampal interneurons that is MLA sensitive and hence belonging to the α7 nAChR subtype (Shao and Yakel 2000). However, the 31-pS channel was not sensitive to MLA, and its molecular identity is therefore unclear. A diversity of nAChRs including α7, α4, and α3 subtypes have been reported in the basal forebrain (Paterson and Nordberg 2000). It is therefore possible that the α7 nAChRs in the basal forebrain may be located on presynaptic terminals as is the case in human cortex and rat striatum (Marchi et al. 2002).

There is increasing evidence that Aβ-nAChR interactions may play an important role in the pathology of AD. The first cholinergic deficits detected in brains of AD patients were reductions in cortical presynaptic cholinergic markers (Bowen et al. 1976; Davies and Maloney 1976; Perry et al. 1977). Although the mechanisms leading to the degeneration of cholinergic neurons are still unclear, there is evidence to link the loss of the basal forebrain cholinergic neurons to memory and cognitive deficits observed in AD patients (Price 1986). Post-mortem analysis of brain tissue from the temporal cortex of AD patients shows a selective loss of the α4, but not α7 or α3, nAChR subunits (Martín-Ruiz et al. 1999; Warman and Nordberg 1995; Wevers et al. 2000). Studies that have examined Aβ...
potential neuroprotective role for nicotinic receptor modulators have yielded conflicting results. In cortical cultures, selective activation of α7 nAChR results in protection against Aβ-induced cell death that is reversed by α-bungarotoxin, an α7 nAChR antagonist (Kihara et al. 1997). However, the same authors report that stimulation of the α4β2 subtype of nAChRs inhibits Aβ toxicity (Kihara et al. 1998). It is important to bear in mind that these studies used Aβ and nicotinic receptor modulators in the μM concentrations, a dose range where a cross-sensitization of the Aβ and α7 nAChR responses has been recently reported in vitro (Dineley et al. 2002). We did not observe any desensitization of the Aβ responses in the dose range of femtomolar to micromolar. The range of effective Aβ doses in our experiments that evoked depolarization in basal forebrain neurons are in keeping with the concentrations of Aβ (high picomolar to nanomolar range) in AD brains and in transgenic animals that overexpress human amyloid precursor protein (Hsia et al. 1999; Kuo et al. 1996). The physio-chemical form of the Aβ used in our study deserves comment. Based on previously published data (Dahlgren et al. 2002) and our method of solubilizing the peptide and using it immediately, we believe that the majority of the Aβ in our study was comprised of the oligomeric form rather than the aggregated fibrillar form of Aβ.

The precise functional role of the Aβ-α4 nAChR interactions is unclear. A recent study suggests that Aβ (at concentrations as low as 10 pM) is a critical requirement for the viability of central neurons (Plant et al. 2003) and thus plays a physiological role. Since our results suggest that Aβ at very low doses (picomolar to femtomolar range) may act as an endogenous ligand at the α4 nAChR, activation of α4 nAChRs may play an important role in survival of neurons. On the other hand, both Aβ25–35 and the longer isoform Aβ1–42, which have been identified as key components within the amyloid plaques in AD brains, could, through an aberrant activation of α4 nAChRs, play an important role in AD. Although α7 nAChRs are highly permeable to calcium (Boyd 1997), prolonged depolarization following Aβ-induced activation of α4 nAChRs could also result in activation of voltage-sensitive calcium conductances which have been described in DBB neurons (Griffith et al. 1994; Jassar et al. 1999). Thus destabilization of calcium homeostasis, which has been postulated to mediate components of Aβ neurotoxicity, could result from Aβ interactions with the α4 or α7 nAChRs. The binding of Aβ to α4 nAChRs may also serve as a portal for internalization of Aβ via the formation of an Aβ-α4 nAChR complex. Such a mode for the intracellular entry and accumulation of Aβ has been described through its binding with the α7 nAChRs (Nagel et al. 2002). Our studies therefore raise the possibility that some of the neurotoxic effects of Aβ may be mediated via activation of the α4 nAChRs possibly resulting in a disturbance of calcium homeostasis. Therefore compounds target this nicotinic receptor may be useful therapeutic strategies for AD.

DISCLOSURES

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