β-Amyloid$_{1-42}$ Peptide Directly Modulates Nicotinic Receptors in the Rat Hippocampal Slice

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Alzheimer's disease (AD) is a human neurological disorder characterized by an increasing loss of cognitive function and the presence of extracellular neuritic plaques composed of the β-amyloid peptide (Aβ_{1-42}). However, the link between these molecular correlates of AD and the loss of cognitive function has not been established. The pathology associated with AD includes the loss of basal forebrain cholinergic neurons, presynaptic terminals in the neocortex and hippocampus, and a decrease in the total amount of neuronal nicotinic acetylcholine receptors (nAChRs). This leads to the hypothesis that failure in the cholinergic system underlies the dementia seen in AD. Cognitive performance has been linked to nAChR function in the hippocampus, and the interneurons expressing nAChRs coordinate the activity of large numbers of principal cells and therefore have a powerful role in the regulation of hippocampal activity. We have found that Aβ_{1-42} inhibits whole-cell and single-channel nicotinic currents from rat hippocampal interneurons by directly blocking the postsynaptic nAChR channels at concentrations as low as 100 nM. This inhibition appears specific for peptide sequence and neuronal nAChRs, and the magnitude of Aβ_{1-42} inhibition is dependent on the nAChR channel subtype expressed. Thus, chronic inhibition of cholinergic signaling by Aβ_{1-42} could contribute to the cognitive deficits associated with AD.

Key words: postsynaptic; photolysis; caged-carbachol; stratum radiatum; interneurons; acetylcholine

Nicotinic acetylcholine receptors (nAChRs) are a multigene family of ligand-gated ion channels (Le Novere and Changeux, 1995; Lindstrom, 1996) that participate in various cognitive brain functions (Levin and Simon, 1998; Jones et al., 1999). Alzheimer's disease (AD) is a human neurological disorder characterized by an increasing loss of cognitive function and accompanied by various deficits in cholinergic neurotransmission, including the loss of cholinergic neurons in the basal forebrain, decrease in release of ACh, and decrease in choline acetyltransferase activity (Auld et al., 1998; Selkoe, 1999). This suggests that impairment of the cholinergic system may occur early in AD and lead to cognitive deficits (James and Nordberg, 1995; Perry et al., 1995; Francis et al., 1999; Paterson and Nordberg, 2000). Other hallmarks of Alzheimer's disease include the presence of extracellular neuritic plaques composed of the β-amyloid peptide (Aβ_{1-42}) and intracellular neurofibrillary tangles composed of tau protein. However, finding the link between these cellular markers and the loss of cognition has remained elusive.

Potential targets in AD pathology are the nAChRs because they are widely expressed throughout the CNS, they are known to participate in cognition, and AD patients exhibit decreased numbers (Le Novere and Changeux, 1995; Levin and Simon, 1998; Jones et al., 1999; Paterson and Nordberg, 2000). Recently, it was reported that Aβ_{1-42} binds the α7 and non-α7 subtypes of nAChRs with high affinity (Wang et al., 2000a,b), but the physiological significance of this binding was not investigated. We have examined the effect of Aβ_{1-42} on nAChR current in the rat hippocampal slice. This region of the brain appears to play a prominent role in cognition, learning, and memory tasks (Stewart and Fox, 1990; Cobb et al., 1999). We determined previously that functional nAChRs are preferentially expressed on the interneurons rather than the principal cells in acute hippocampal slices (Jones and Yakel, 1997). Here we demonstrate that Aβ_{1-42} inhibits these responses by directly blocking the postsynaptic nAChR channels. Chronic inhibition of cholinergic signaling by Aβ_{1-42} could contribute to the cognitive deficits and loss of cholinergic function associated with Alzheimer's disease.

MATERIALS AND METHODS

Slice preparation. Standard techniques were used to prepare 400-μm-thick slices from the hippocampus of 13- to 18-d-old rats (Jones et al., 1999) and to make whole-cell patch-clamp recordings from CA1 stratum radiatum interneurons. Pipettes were filled with a solution that contained (in mM): 100 gluconic acid, 2–10 EGTA, 5 $MgCl_2$, 2 Mg-ATP, 0.3 GTP, 40 HEPES; pH to 7.2 with CsOH. Slices were superfused at 21°C with oxygenated physiological saline containing (in mM): 119 NaCl, 2.5 KCl,

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1.3 $MgCl_2$, 2.5 $CaCl_2$, 1 NaH_2PO_4, 26.2 $NaHCO_3$, 11 glucose, and either caged-glutamate or caged-carbachol (50 μM) (Molecular Probes, Eugene, OR) (Milburn et al., 1989). In some experiments, 10 μM atropine was also added to block muscarinic AChR mediated responses. In photolysis experiments, dose–response curves were constructed by adding $A\beta_{1-42}$ or $A\beta_{12-28}$ (RBI/Sigma, St. Louis, MO; prepared just before use) peptide incrementally to increase the concentration from 250 to 500 nM, 1 μM, and 2 μM. Data were normalized relative to the amplitude of the initial response. Recordings were analyzed only if the holding current was <100 pA when cells were voltage-clamped at −70 mV.

To eliminate the possibility that the caged-carbachol could itself desensitize nAChRs, nAChR-mediated synaptic transmission was elicited by electrical stimulation followed by the addition of 50 μM caged-carbachol to the bath solution. The caged-carbachol had no effect on the amplitude of the synaptic responses, suggesting that it did not desensitize nAChRs (data not shown). For pressure application experiments, ACh was applied using the Burleigh PZ-150M piezo electric device. ACh (1 mM for 3 sec) was used to elicit nAChR currents at 3 min intervals. Dose–response curves were constructed by switching from ACh to ACh/$A\beta_{1-42}$ solutions containing 50, 100, 250, 500 nM, and 1 μM $A\beta_{1-42}$. To test for reversal of the $A\beta_{1-42}$ inhibition, we then switched back to the ACh solution.

Local photolysis. The 351–364 nm output of a continuous emission 8 W argon ion laser (Spectraphysics Model 165) was delivered, via a multimode optical fiber, through an Olympus 40× water-immersion objective to form an uncaging spot 7.5 μm in diameter. An electronic shutter (Uniblitz) was used to vary the duration of the light pulse (2–6 msec). The uncaging spot was positioned over a cellular process by including a fluorescent dye (Oregon Green-1, 200 μM; Molecular Probes) in the patch pipette solution and then visualizing the cell with a cooled CCD camera (Sensicam). To avoid possible phototoxic effects, illumination was kept to a minimum.

Single-channel recordings. The single-channel outside-out patch-clamp configuration was used to pull patches from the soma of hippocampal CA1 stratum radiatum interneurons (Shao and Yakel, 2000). Pipettes had resistances of 5–10 MΩ when back-filled with pipette solution containing (in mM): 140 cesium gluconate, 10 HEPES, 2 $MgCl_2$, 0.5 $CaCl_2$, 5 BAPTA, and 2 Mg-ATP, pH 7.2 adjusted with CsOH. Single-channel currents were obtained using an Axopatch 200B amplifier (Axon Instruments), low-pass-filtered at 5 kHz, and digitized at 20 kHz. All data were acquired and analyzed with pClamp 8 software (Axon Instruments). The average amplitudes of single-channel currents were measured using an all-points histogram well fitted by Gaussian distributions. The open channel probability (P_o) was estimated from the event lists determined with the Fetchan program. The detection of events was determined by the "50% threshold" method. Data were collected from a total of eight patches from eight cells. Single-channel measurements were made by sampling for 3–10 sec for each patch and each condition.

RESULTS

The nicotinic responses of CA1 interneurons in slices of rat hippocampus desensitize rapidly, particularly the α7 receptor subtype (Alkondon et al., 1997; Jones and Yakel, 1997; Frazier et al., 1998a; Ji and Dani, 2000). Therefore, we chose to elicit nicotinic currents from stratum radiatum interneurons by local photolysis (Wang and Augustine, 1995; Pettit et al., 1997) of caged-carbachol (50 μM). This method allows us to isolate postsynaptic nAChRs (Alkondon et al., 1998; Frazier et al., 1998b) and induce rapid, brief activation of nAChRs with minimal desensitization. Brief pulses (2–5 msec) of UV light were delivered from a continuous emission argon ion laser at 3 min intervals, under whole-cell voltage-clamp conditions.

All caged-carbachol-induced currents can be blocked by curare (10 μM) and high, nonselective concentrations of methyllycaconitine (MLA; 500 nM), demonstrating that they are caused by activation of nAChRs. Many of these currents require both 50 nM MLA and dihydro-β-erythroidine (10 μM) for complete block, suggesting that they are caused by activation of both α7 and non-α7 subtypes of nAChRs. However, some currents are completely blocked by 50 nM MLA (Fig. 1*A*). Previously published single-channel and whole-cell nAChR data suggest that ~70% of the nAChRs on interneuron cell bodies are the α7 subtype, whereas 30% are the non-α7 subtype (Jones and Yakel, 1997; Shao and Yakel, 2000). These data suggest that only nAChR-mediated currents are evoked by uncaging caged-carbachol and that diverse subtypes (i.e., both α7 and non-α7) are being activated (Fig. 1*A*).

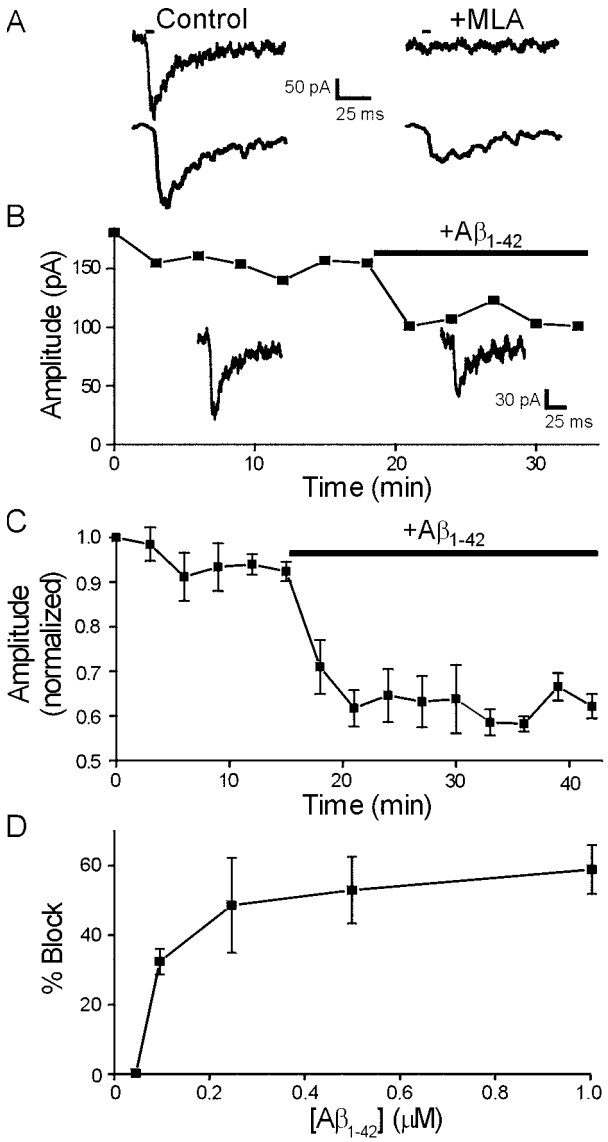

Figure 1. $A\beta_{1-42}$ blocks current through nAChRs. *A*, Nicotinic currents evoked by local photolysis of caged-carbachol. Some currents are completely blocked by application of 50 nM MLA (*top*) and some are only partially blocked (*bottom*). *B*, Plot of nicotinic current amplitude during control period and after application of $A\beta_{1-42}$ (2 μM). *C*, Averaged response amplitude before and after application of 2 μM $A\beta_{1-42}$ ($n = 5$). *D*, The block of nicotinic current is dose dependent. Averaged amount of block elicited by varying concentrations of $A\beta_{1-42}$ ($n = 3$). Whole-cell currents were elicited by pressure application of 1 mM ACh and $A\beta_{1-42}$.

$A\beta_{1-42}$ inhibits carbachol-induced current

Does the binding of $A\beta_{1-42}$ to nAChRs affect current through these receptors? An initial application of $A\beta_{1-42}$ (1 μM) reduced current amplitude by 40% when added to the perfusate after a baseline response was established (Fig. 1*B*,*C*). The addition of a higher dose of $A\beta_{1-42}$ (2 μM) produced no further increase in the current block. We subsequently determined that block of nAChRs by $A\beta_{1-42}$ was dose dependent, with a maximum of 39 ±

3% at a dose of 500 nM. Application of a lower dose (250 nM) of the peptide produced a 20 ± 3% block. We have also examined the effect of $A\beta_{1-42}$ on whole-cell nicotinic currents elicited by pressure application of ACh and $A\beta_{1-42}$. Using this method, nAChR currents were also inhibited in a dose-dependent manner (Fig. 1*D*). At 50 nM, $A\beta_{1-42}$ had no effect on current amplitude, but a concentration of 100 nM inhibited currents by 32 ± 4%. Pressure application of $A\beta_{1-42}$ produced a higher level of inhibition, 59 ± 7% (Fig. 1*D*) ($n = 3$), at a concentration of 1 μM when compared with 35 ± 5% ($n = 4$) with the uncaging method. It is possible that the higher doses of ACh delivered by pressure application (as evidenced by currents lasting tens of seconds) may have produced some receptor desensitization, which contributed to this discrepancy. Together these data are consistent with high-affinity binding of $A\beta_{1-42}$ to nAChRs that leads to an inhibition of postsynaptic nAChR-mediated current.

$A\beta_{1-42}$ inhibition is reversible

The inhibition of nAChR currents by $A\beta_{1-42}$ is rapidly reversible under whole-cell conditions. Figure 2*A* illustrates an experiment in which nicotinic whole-cell currents were elicited from hippocampal slice interneurons by pressure application of 1 mM ACh. After a baseline was established, ACh + $A\beta_{1-42}$ (50 nM) were applied, inhibiting the whole-cell current by 40%. After the removal of $A\beta_{1-42}$, complete recovery occurred within 6 min (Fig. 2*A*). The total amount of recovery varied between cells from 60 to 100%.

$A\beta_{12-28}$ also inhibits carbachol-induced current

To explore which region of $A\beta_{1-42}$ inhibits nAChRs, we tested the ability of a peptide fragment, $A\beta_{12-28}$, to block nAChR current. Previous work has demonstrated that $A\beta_{12-28}$ interferes with the binding of $A\beta_{1-42}$ to the nAChRs (Wang et al., 2000a). $A\beta_{12-28}$ was also able to inhibit current amplitude in a dose-dependent manner (Fig. 2*B*). The maximal amount of current block was increased to 95 ± 2% (Fig. 2*B*) ($n = 5$). The apparent increased effectiveness of the short peptide may be caused by differences in binding affinity, or it may reflect better access of the shorter peptide to the extracellular space within the slice. Taken together, these data demonstrate that $A\beta_{1-42}$ directly modulates postsynaptic nAChRs and that this modulation is mediated by the fragment including amino acid residues 12–28.

$A\beta_{1-42}$ inhibition is specific for peptide sequence and nicotinic receptors

We next examined whether $A\beta_{1-42}$ inhibited nAChRs by a direct postsynaptic interaction or through nonspecific interactions. First, the specificity of amino acid sequence was tested. A 40 amino acid peptide with a sequence that was the reverse of $A\beta_{1-42}$ was used. $A\beta_{40-1}$ had no effect on carbachol-induced current amplitude (Fig. 2*C*) ($n = 3$). This is in accord with previous work demonstrating that $A\beta_{40-1}$ does not mimic the effects of $A\beta_{1-42}$ (Auld et al., 1998). In a further test of specificity, we examined the ability of $A\beta_{1-42}$ to modulate ligand-gated ion channels other than nAChRs. $A\beta_{1-42}$ (2 μM) had no effect on the amplitude or time course of currents elicited by local photolysis of caged-glutamate (Fig. 2*D*) ($n = 4$). The inability of $A\beta_{1-42}$ to modulate glutamate currents and the ineffectiveness of $A\beta_{40-1}$ indicates that block of current amplitude by $A\beta_{1-42}$ is specific for nAChRs and peptide sequence. Because carbachol activates both muscarinic and nicotinic receptor types, we also tested whether the observed inhibition of current occurred through a muscarinic receptor-associated pathway. In some experiments, 10 μM atropine was used to block muscarinic receptors. Atropine had no effect on the inhibition of nicotinic currents by $A\beta_{1-42}$ (data not shown). These data further support a direct, inhibitory interaction of $A\beta_{1-42}$ with postsynaptic nAChRs.

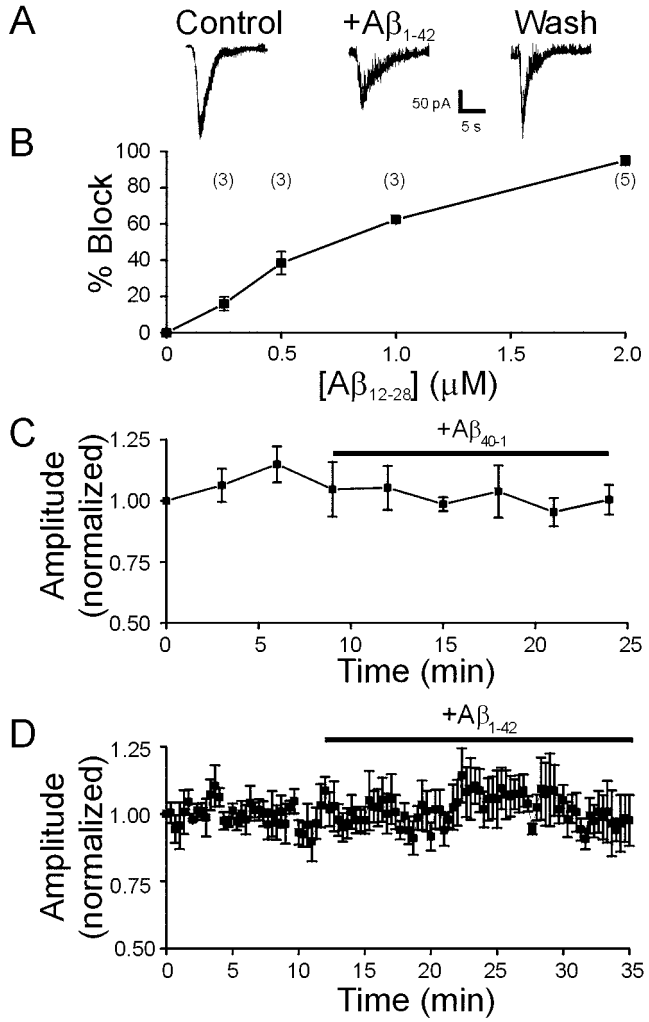

Figure 2. $A\beta_{1-42}$ block is reversible, specific, and mimicked by the truncated peptide $A\beta_{12-28}$. *A*, The inhibition of whole-cell currents by $A\beta_{1-42}$ is reversible. Individual responses were elicited by either ACh or ACh + $A\beta_{1-42}$ (100 nM). Complete reversal of the block was observed 6 min after removal of $A\beta_{1-42}$. *B*, $A\beta_{12-28}$ blocks currents elicited by uncaging caged-carbachol in a dose-dependent manner. *C*, Nicotinic currents induced by local photolysis of caged-carbachol are not affected by 2 μM $A\beta_{40-1}$. D, $A\beta_{1-42}$ (2 μM) does not affect glutamate currents evoked by local photolysis of caged-glutamate (15 sec intervals).

$A\beta_{1-42}$ decreases open channel probability of nAChRs

To investigate the mechanism of current block by $A\beta_{1-42}$, we examined its effect on the single-channel properties of nAChRs in outside-out patches that were excised from stratum radiatum interneurons in hippocampal slices (Shao and Yakel, 2000). Channels were activated by pressure application of 10 μM ACh for 30 sec. We observed two different channel types: one with a single-channel conductance of 38 pS and another with a 62 pS conductance (Fig. 3*A*). $A\beta_{1-42}$ (2 μM) reduced the P_o of both channel types within milliseconds of ACh application. The block was partially reversible, probably because of channel rundown (Fig. 3*A*) (Shao and Yakel, 2000). These data further support the hypothesis that $A\beta_{1-42}$ inhibits nAChR current by binding directly to nAChRs with high affinity and specificity.

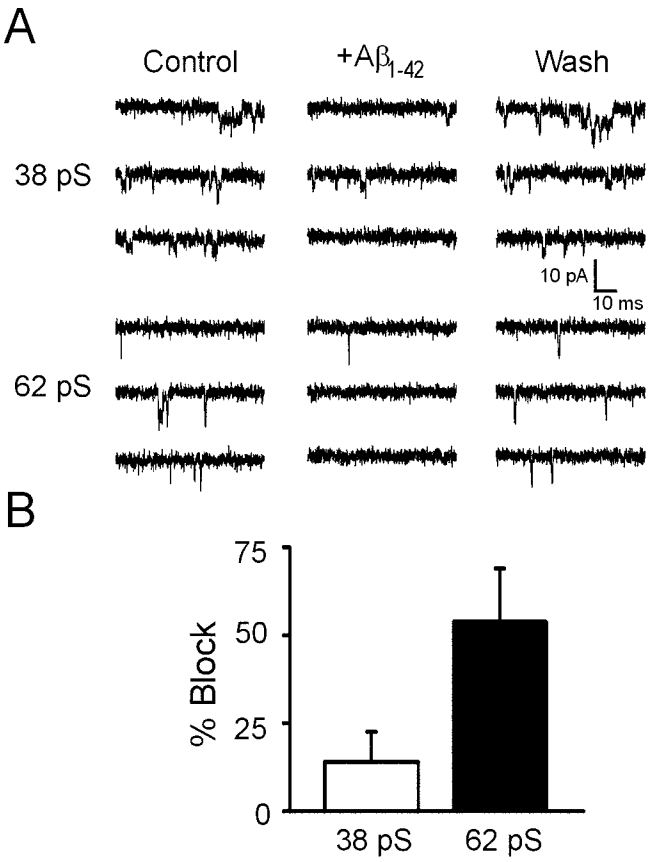

Figure 3. $A\beta_{1-42}$ reduces nAChR open channel probability. *A*, Single-channel responses to ACh (10 μM) before, during, and after application of 2 μM $A\beta_{1-42}$ for both channel types. For the 38 pS channel, P_o was 0.2 (*Control*), 0.15 ($+A\beta_{1-42}$), and 0.17 (*Wash*). For the 62 pS channel, P_o was 0.006 (*Control*), 0.003 ($+A\beta_{1-42}$), and 0.004 (*Wash*). *B*, Average block of P_o after application of $A\beta_{1-42}$ for both channel types. The frequency of channel opening (sec^{-1}) for the 38 pS channel before, during, and after $A\beta_{1-42}$ application was 870 ± 550, 707 ± 420, and 1150 ± 740, respectively. For the 62 pS channel, these values were 77 ± 30, 45 ± 20, and 50 ± 20, respectively.

The magnitude of the inhibition is dependent on the receptor subtype expressed

To determine the nAChR subtype composition and sensitivity to $A\beta_{1-42}$, we applied the α7-specific antagonist MLA (50 nM) to excised patches. As expected from our previous work (Shao and Yakel, 2000), activation of the 38 pS channel by ACh (10 μM) was sensitive to MLA, indicating that it contained the α7 nAChR subunit. The 62 pS channel was insensitive to block by MLA, suggesting that this channel did not contain the α7 subunit. $A\beta_{1-42}$ effectively decreased the P_o at both α7 and non-α7 subtypes, consistent with the idea that $A\beta_{1-42}$ binds and inhibits multiple subtypes of nAChRs (Fig. 3*B*) (Wang et al., 2000b). However, the magnitude of channel inhibition was dependent on the receptor subtype. $A\beta_{1-42}$ reduced P_o of the 38 pS channel by 14 ± 8% ($n = 5$) while P_o of the 62 pS channel was reduced by 54 ± 15% (Fig. 3*B*) ($n = 3$). The frequency of channel opening was also decreased by 16 ± 9% and 32 ± 20%, respectively. The decrease in channel block by $A\beta_{1-42}$ for the 38 pS channel was significantly different from that of the 62 pS channel ($p < 0.05$; Student's *t* test). On the basis of our previous work as well as the current study, we found that 70% of the nAChRs are the 38 pS (MLA sensitive) subtype and 30% are the 62 pS subtype. Assuming that the channels are coexpressed on most neurons, as suggested by our whole-cell data, we would predict an inhibition of 26% [(0.70 × 0.14) + (0.30 × 0.54)]. The average observed inhibition of the carbachol-induced currents was 39 ± 3%, which appears somewhat larger, but it is possible that we have underestimated the level of α7 inhibition because channels in patches may not be regulated in the same fashion as channels in the whole-cell configuration.

DISCUSSION

We have provided evidence of a novel physiological role for $A\beta_{1-42}$ as an inhibitor of postsynaptic nAChRs in rat hippocampal interneurons. $A\beta_{1-42}$ blocked nAChR-mediated current and reduced open channel probability. The inhibition of nAChR-mediated current is specific for $A\beta_{1-42}$ and nAChRs, suggesting a direct modulation of nAChRs, probably through the amino acid residues 12–28 of $A\beta_{1-42}$. This modulation occurs rapidly, within milliseconds at single channels, and in <3 min in brain slices. The amount of inhibition is dependent on the subtype of receptor being expressed. Together these data are consistent with high-affinity binding of $A\beta_{1-42}$ to nAChRs that leads to an inhibition of postsynaptic nAChR-mediated current. Because expression of nicotinic receptor subtypes in the brain can vary with genetic patterns and environmental exposure (Slotkin, 1998), the susceptibility to block by $A\beta_{1-42}$ may also vary from individual to individual.

$A\beta_{1-42}$ was an effective inhibitor of nicotinic currents at concentrations as low as 100 nM. The physiological relevance of this concentration depends on two factors: (1) the actual concentration of $A\beta_{1-42}$ within the brain slices and (2) the concentration of $A\beta_{1-42}$ in AD brain tissue. Both of these factors are difficult to determine with a high degree of certainty. We were unable to determine the exact $A\beta_{1-42}$ concentration within the brain slice tissue, but it is likely that $A\beta_{1-42}$ concentration is significantly lower than that of the bath solution because of restricted diffusion and access to the extracellular space. Accurate estimates of $A\beta_{1-42}$ concentrations in AD brain tissue are also difficult to determine, but transgenic animals expressing mutant forms of human amyloid precursor protein have Aβ concentrations estimated in the low nanomole range (10–50 nM) (Hsia et al., 1999; Mucke et al., 2000). However, this measure may be an underestimate of $A\beta_{1-42}$ concentration because these values were determined with a global tissue assay. Aβ distribution is unlikely to be completely random and uniform throughout the brain. As a result, concentrations in targeted regions of the brain or at synaptic release sites may be much higher.

Previously published binding data (Wang et al., 2000a,b) suggests that $A\beta_{1-42}$ binds to nAChRs in the low picomole range for α7 and in the 20–30 nM range for non-α7 nAChRs. We observed inhibition of the non-α7 receptors at concentrations only three- to fivefold higher than the binding data. However, ligand-binding measurements do not access function. Many receptors require the binding of multiple ligands before channels open, and binding affinity is often dependent on the receptor state (Chang and Weiss, 1999). Standard binding assays usually use membrane preparations that may alter the regulation and conformation of the channels. Taken together with the uncertainty of actual tissue levels of $A\beta_{1-42}$, our effective concentrations are consistent with the binding data for non-α7 receptor subtypes. The extremely high-affinity binding reported for α7 is more difficult to reconcile.

We currently favor a direct mechanism of action by $A\beta_{1-42}$ because of its effect on excised, outside-out, cell-free membrane patches, and the direct binding to multiple subtypes of nAChR

channels previously demonstrated (Wang et al., 2000b). Other mechanisms of action are possible through various different signal transduction cascades known to be regulated by $A\beta_{1-42}$ (e.g., G-protein and free radical pathways). However, such pathways are unlikely to be functioning in our excised patches.

It remains unclear which form of $A\beta_{1-42}$ (i.e., fibrillar vs soluble) is toxic. Initial reports suggested that only fibrillar amyloid was neurotoxic (Lorenzo and Yankner, 1994), but recent evidence (Roher et al., 1996) suggests that it is the soluble oligomeric form of Aβ that may be neurotoxic. We are unable to conclusively state which form of $A\beta_{1-42}$ is binding to nAChRs in our experiments. Because we prepared our $A\beta_{1-42}$ solutions just before use, and because the fibrillar form of $A\beta_{1-42}$ would have very poor access to the extracellular space in brain slice tissue, we believe that the nAChRs are inhibited by the soluble, oligomeric form of $A\beta_{1-42}$. The very rapid onset of the inhibition at single channels (20 msec) is also consistent with this hypothesis.

Our results may provide a mechanistic explanation for the early cognitive deficits seen in AD patients long before plaque formation (Hsia et al., 1999; Naslund et al., 2000). Early cognitive effects have also been seen in transgenic animals in which behavioral deficits precede amyloid deposition, and some individuals have neuritic plaques without the cognitive deficits associated with AD (Hardy, 1997). $A\beta_{1-42}$ also inhibits the best-characterized form of cellular learning and memory: long-term potentiation (Chen et al., 2000). All of these data suggest that $A\beta_{1-42}$ might exert its cognitive effects independently of plaque formation (Naslund et al., 2000). In contrast, the neurotoxic effects of $A\beta_{1-42}$ are often associated with the fibrillar form [but see Roher et al. (1996); Auld et al. (1998)]. Initiation of neurotoxic events usually requires longer exposures and higher doses of $A\beta_{1-42}$, probably initiating a number of signal transduction pathways that may differ from those underlying cognitive impairment.

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