Amyloid β-Peptide Aβ₁₋₄₂ But Not Aβ₁₋₄₀ Attenuates Synaptic AMPA Receptor Function

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ABSTRACT The brains of Alzheimer’s disease (AD) patients have large numbers of plaques that contain amyloid beta (Aβ) peptides which are believed to play a pivotal role in AD pathology. Several lines of evidence have established the inhibitory role of Aβ peptides on hippocampal memory encoding, a process that relies heavily on α-aminon-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor function. In this study the modulatory effects of the two major Aβ peptides, Aβ₁₋₄₀ and Aβ₁₋₄₂, on synaptic AMPA receptor function was investigated utilizing the whole cell patch clamp technique and analyses of single channel properties of synaptic AMPA receptors. Bath application of Aβ₁₋₄₂ but not Aβ₁₋₄₀ reduced both the amplitude and frequency of AMPA receptor mediated excitatory postsynaptic currents in hippocampal CA1 pyramidal neurons by ~60% and ~45%, respectively, in hippocampal CA1 pyramidal neurons. Furthermore, experiments with single synaptic AMPA receptors reconstituted in artificial lipid bilayers showed that Aβ₁₋₄₂ reduced the channel open probability by ~42% and channel open time by ~65% and increased the close times by several fold. Aβ₁₋₄₀, however, did not show such inhibitory effects on single channel properties. Application of the reverse sequence peptide Aβ₂₋₄₁ also did not alter the mEPSC or single channel properties. These results suggest that Aβ₁₋₄₂ but not Aβ₁₋₄₀ closely interacts with and exhibits inhibitory effects on synaptic AMPA receptors and may contribute to the memory impairment observed in AD. Synapse 61:367–374, 2007.

INTRODUCTION Alzheimer’s disease (AD) is the most common form of dementia in elderly, affecting 4.5 million people in the United States alone (Hebert et al., 2003). AD is characterized by the progressive formation of senile plaques, which precede cognitive decline. These plaques are composed of large amounts of amyloid beta peptides (Aβ) (Bayer et al., 2001), which are the cleavage products of amyloid precursor protein (APP), a presynaptic terminal protein with a large extracellular domain. The plaques mainly consist of accumulated Aβ₁₋₄₀ and Aβ₁₋₄₂ (Glenner and Wong, 1984; Masters et al., 1985), which are widely believed to contribute to neurotoxicity and AD pathogenesis (Selkoe, 2000). Aβ can induce neurotoxicity in various model systems (Hölscher, 1998), and the toxic effect involves a varied cascade of mechanisms (Clippingdale et al., 2001). Early stages of AD pathophysiology are largely associated with the medial temporal lobe, especially the hippocampus (Laakso, 2002), and accordingly most patients diagnosed early with AD show remarkable deficits in hippocampus dependent memory forms, (Rowan et al., 2004) strengthening the notion that the hippocampus is the major brain region affected by AD pathology.

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The mechanisms that involve memory deficits, which precede remarkable neuronal loss that continues progressively throughout the disease, may involve relevant receptor deregulation and a subsequent decline in synaptic plasticity (Szegedi et al., 2005). Several reports have indicated that perfusion of the hippocampus with high nanomolar to low micromolar concentrations of Aβ peptides (Aβ1–40, Aβ1–42, Aβ25–35) can inhibit long term potentiation (LTP) (Chen et al., 2000; Cullen et al., 1997; Freir et al., 2001; Itoh et al., 1999; Lambert et al., 1998; Ye and Qiao, 1999), a cellular correlate for memory. Additionally, deficits in LTP have also been reported to correlate with the accumulation of intraneuronal Aβ (Oddo et al., 2003). Furthermore, soluble Aβ1–42 has been shown to inhibit LTP and is believed to be involved in the pathogenesis of AD that precedes cellular death and cognitive decline (Chang et al., 2006). These reports support the now well accepted inhibitory role of Aβ peptides in memory processes.

Induction and expression of LTP depends on the regulated activity of ionotropic glutamate receptors, N-methyl-D-aspartate (NMDA) receptors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Muller et al., 1988). Since several reports have shown that LTP is inhibited by Aβ peptides, many studies have specifically addressed the effects of these peptides on glutamate receptors, particularly the NMDA receptor function. Previous studies have shown that in the dentate gyrus of rat and mouse models, the induction of NMDA receptor-dependent LTP is inhibited by Aβ1–42 (Wang et al., 2004), while Aβ1–40 has been shown to inhibit NMDA receptor mediated synaptic potentials in the rat hippocampus (Raymond et al., 2003). In contrast, quantitative studies of synaptic potentials have revealed that Aβ1–40 enhances NMDA receptor mediated currents in dentate granule cells (Wu et al., 1995). Although recent studies have implicated potential AMPA receptor downregulation (Chang et al., 2006; Shemer et al., 2006), the effect of Aβ on AMPA receptor function is not clearly understood due to a scarcity of research reports addressing this issue. Since AMPA receptors are essential for LTP and their potentiation is required for activation of NMDA receptors (Watt et al., 2004), we hypothesize that the comprehensive neurotoxic mechanism of Aβ may include modulation of synaptic AMPA receptor function. To determine whether Aβ has the potential to modulate synaptic AMPA receptor properties, we examined the effect of acute exposure of Aβ1–40 and Aβ1–42 on AMPA receptor mediated miniature excitatory postsynaptic currents (mEPSCs) in cultured rat hippocampal slices. Additionally, we examined the effect of Aβ on the single channel properties of synaptic AMPA receptors by utilizing adult rat hippocampal synaptosomes reconstituted in artificial lipid bilayers. Results of this study show for the first time that Aβ1–42, which accumulates during the development of AD, can potently modulate AMPA receptors, and may play a major role in memory impairment associated with AD.

**MATERIALS AND METHODS**

**Preparation of organotypic hippocampal slice cultures and whole cell recordings**

Organotypic hippocampal slice cultures were prepared using the method originally described by Stoppini (1991) with some modifications. Briefly, the whole brains were rapidly dissected out from Sprague–Dawley rats aged 5–7 days, placed in ice cold Hank's balanced salt solution, and then sliced into sections of 400 μm in thickness using a tissue slicing system (Vibratome 1000 series, Warner Instruments, Hamden, CT). The hippocampal slices were isolated from other tissues and were placed at the air-medium interface of humidified semiporous (0.4 μm) Millicell® membrane inserts (Millipore Corp., Bedford, MA), which in turn were placed on a six-well culture plate (Falcon Multiwell, Becton Dickinson, Franklin Lakes, NJ) containing 1 ml of culture media in each well. The culture media contained 25% Earle’s balanced salt solution, 30% MEM, 5% heat-inactivated horse serum, and was supplemented with 1 mM glutamine, 36 mM glucose, antibiotic (Streptomycin, 1.0/100 ml), and antifungal (Fungizone, 0.5/100 ml) solutions. Prior to use, the culture media was sterile filtered with 0.22-μm pore filters. Cultures were maintained in an incubator at 36°C, 100% humidity, and 5% carbon dioxide and the media was changed every other day.

Nine-day-old cultured slices were selected for whole cell recordings. Individual organotypic slices were transferred to the recording chamber fitted on the stage of a microscope (Olympus BX51WI; Olympus America, Center Valley, PA) with water immersion differential interphase contrast objectives. The slices were continuously superfused at a steady rate with artificial cerebrospinal fluid (ACSF) containing in millimolar: NaCl, 119; KCl, 2.5; MgSO4, 1.3; CaCl2, 2.5; NaH2PO4, 1.0; NaHCO3, 26.0; and dextrose 11.0 gassed with 95% O2:5% CO2. Pyramidal neurons from the CA1 region were identified and whole cell recordings were made with a pipette (7–10 MΩ resistance) filled with solution containing in millimolar: K-glucosinate, 100; EGTA, 0.6; MgCl2, 5.0; Na-ATP, 2.0; Na-GTP, 0.3; and HEPES 40. AMPA receptor mediated excitatory mEPSCs were isolated by the addition of tetrodotoxin (TTX, 1.0 μM), picrotoxin (PTX, 50 μM) and DL-2-amino-5-phosphono pentanoic acid (APV, 100 μM) to the ACSF. Cells were voltage clamped at –80 mV with an Axopatch 200B amplifier (Molecular Devices Corp., Sunnyvale, CA). To be included for analysis, the currents had to be greater than 3 pA.
but less than 100 pA and series resistances between 20 and 30 MΩ with drifts less than 15%. At the end of each experiment, 30 µM CNQX was added to block the AMPA receptor mediated mEPSCs. The currents were low bypass filtered at 2 kHz, digitized, acquired using pClamp 8 software program (Molecular Devices, Sunnyvale, CA), and stored in computer disks for offline analysis.

**Synaptosome preparation and single channel current recordings**

Isolation of synaptosomes was carried out as described in Johnson et al. (1997) with some modifications. Briefly, adult (4 to 9-months old) Sprague–Dawley rats were anesthetized, the brains were removed and placed in ice cold ACSF, and the hippocampi were isolated and stored at −80°C. Hippocampi were then homogenized (10 strokes) in a Potter homogenizer and in ice cold modified Krebs–Henseleit buffer (mKRBS) containing in millimolar: NaCl, 118.5; KCl, 4.7; MgSO₄, 1.18; CaCl₂, 2.5; KH₂PO₄, 1.18; NaHCO₃, 24.9; dextrose, 10; adenosine deaminase, 10 µg/ml; pH adjusted to 7.4 by bubbling with 95% O₂:5% CO₂. Protease inhibitors, leupeptin (0.01 µg/ml), pepstatin A (0.005 mg/ml), aprotinin (0.1 mg/ml), and benzamidine (5 mM) were included in the buffer to minimize proteolysis. Then the homogenate was diluted with 500 µl of additional ice cold mKRBS buffer. This mixture was loaded in a 1 cm³ syringe and was forced through a 100 µm pore cell strainer (BD Falcon, Bedford, MA) prewetted with 150 µl of mKRBS, and collected in an eppendorf tube. This filtered mixture was loaded into another 1 cm³ syringe and filtered through a prewetted 5 µm pore low protein binding filter (Millex-SV; Millipore Corp., Bedford, MA). The homogenate was kept in ice cold temperatures during the entire procedure to minimize proteolysis. The filtered mixture was then spun at 1000g for 15 min in a microcentrifuge at 4°C. The supernatant was removed and the pellets rich in synaptosomes were resuspended in 50 µl of mKRBS and stored at −80°C for further use.

Experimental procedure for recording single channel AMPA receptor currents from synaptosomes has been described previously (Vaithianathan et al., 2005). Briefly, synaptosomal AMPA receptors were incorporated into artificial lipid bilayers using tip–dip method (Coronado and Lattore, 1983). The bilayers were formed by the successive transfer of two monolayers. The pipette (100 MΩ) and bath solutions contained pseudo-intra and -extra cellular solutions, respectively. The intracellular solution contained in millimolar: KCl, 110.0; NaCl, 4.0; NaHCO₃, 2.0; CaCl₂, 0.1; MgCl₂, 1.0; and 3-N-morpholino propane sulfonic acid 2.0 with pH adjusted to 7.4 and the extracellular solution contained in millimolar: NaCl, 125.0; KCl, 5.0; NaH₂PO₄, 1.25; Tris–HCl, 5.0; and pH adjusted to 7.4. Addition of 2 µl of synaptosomal suspension to the extracellular solution and gentle stirring resulted in fusion of synaptosomal fragments to the lipid bilayer. AMPA receptor single channel currents were evoked and isolated by adding AMPA (290 nM), tetrodotoxin (1 µM), tetraethyammonium chloride (2 µM), APV (50 µM), methyl glutamate analog (2S, 4R)-4-methylglutamate (SYM 2081; 1 µM), and PTX (100 µM). At the end of all experiments, specific AMPA receptor antagonist SYM 2206 (1 µM) was added to confirm the single channel currents recorded were AMPA receptor currents. Single channel AMPA currents were low bypass filtered at 2 kHz, sampled at 20 kHz, digitized, recorded online in video tapes and subsequently saved in computer disks for offline analysis. Only experiments in which single channel currents were completely blocked by SYM 2206 were used for analysis.

**Application of Aβ peptides**

After recording continuous traces of AMPA receptor mediated mEPSCs or single channel currents for 5–10 min, and if the currents were consistent the Aβ peptides, Aβ₁₋₄₂ or Aβ₁₋₄₀ or the reverse peptide Aβ₄₂₋₁ was infused into the ACSF. Aβ peptides were dissolved in deionized water to make stock solutions, which were divided into small aliquots and flash frozen at −80°C. This process yields soluble monomers of Aβ peptides (Nichols et al., 2005). After adding the Aβ peptide, AMPA receptor currents were recorded for 30 min or more. The Aβ peptides were then washed out and the AMPA receptor currents were measured. Ion channel blockers were purchased from Tocris Cookson (Ellisville, MO). Amyloid β peptides were purchased from Sigma and Bachem (Sigma Chemicals, St. Louis, MO; Bachem Bioscience, King of Prussia, PA). Unless specified all other chemicals were purchased either from Fisher Scientific or Sigma.

**Data analysis**

For single channel analysis, only patches exhibiting long stretches of current transitions were selected. The single channel currents were analyzed with pClamp 9.0 software (Molecular Devices, Sunnyvale, CA). Log transformed open and closed time histograms were fitted best with two and three terms by exponential log probability variable metric method. Current amplitude histograms were fitted with two-term Gaussian fit using the Microcal Origin program. Whole cell mEPSCs were analyzed with the Mini Analysis program (Synaptosoft, Fort Lee, NJ). The data are reported as means ± SEMs. One-way analysis of variance was applied to test for the statistical significance. Statistical significance is defined as P < 0.05.

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RESULTS

AMPA receptor mEPSCs are modulated by Aβ₁₋₄₂ but not by Aβ₁₋₄₀

To examine the effect of Aβ peptides on AMPA receptor mediated synaptic currents, AMPA receptor mediated mEPSCs were recorded from CA1 pyramidal cells in the presence of TTX (1.0 μM), PTX (50 μM), and APV (100 μM) (Fig. 1Ai). The Aβ peptides (1.4 μM) were infused to the ACSF during mEPSC recordings, and the changes in mEPSC amplitudes and frequencies were analyzed. We chose the effective minimum concentration of 1.4 μM since both Aβ peptides can form aggregates at high micromolar concentrations (Chen and Glabe, 2006). The mean amplitude of mEPSCs prior to Aβ application was 16.68 ± 1.23 pA (n = 12; Figs. 1Ai and 1C), and was significantly decreased to 6.98 ± 0.07 pA when Aβ₁₋₄₂ was applied (P < 0.05, n = 12; Figs. 1Aii and 1C). In contrast, application of Aβ₁₋₄₀ did not result in any significant changes in the amplitude (16.14 ± 0.86 pA, n = 9; Figs. 1Aiii and 1C). Application of the control reverse peptide Aβ₄₂₋₁ also did not cause any changes in amplitude (16.39 ± 0.91 pA, n = 9; Figs. 1Aiv and 1C).

In addition to the reduction in amplitude, the decay time of mEPSCs (control, 9.3 ± 2.01 ms) showed a decrease upon application of Aβ₁₋₄₂ (6.6 ± 1.20 ms, P < 0.05), while application of Aβ₁₋₄₀ did not affect the decay time (9.4 ± 2.19 ms). The frequency of mEPSCs was significantly diminished upon application of Aβ₁₋₄₂ (0.15 ± 0.014 Hz, n = 12, P < 0.05; Figs. 1Aii and 1D) when compared to controls (0.28 ± 0.024 Hz, n = 12). After washing out Aβ₁₋₄₂, the amplitude and frequency of mEPSCs returned to control values (data not shown). The application of Aβ₁₋₄₀ did not affect mEPSC frequency (0.27 ± 0.015 Hz, n = 9; Figs. 1Aiii and 1D). Similarly, application of Aβ₄₂₋₁ also did not affect mEPSC frequency (0.27 ± 0.031 Hz, n = 9; Figs. 1Aiv and 1D).

Modulation of single channel properties of synaptic AMPA receptors by Aβ₁₋₄₂ but not by Aβ₁₋₄₀

Western immunoblot analysis was performed to ensure that the synaptosomal preparations used were enriched with AMPA receptors. The results of the Western immunoblot analysis revealed that the synaptosomes were indeed highly concentrated in both postsynaptic fractions and the AMPA receptor subunit GluR1 when compared to the whole brain preparation (data not shown). This is in agreement with our previous study on the characterization of synaptosomal AMPA receptors (Vaithianathan et al., 2005).

The single channel activities of synaptic AMPA receptors were elicited by addition of 290 nM AMPA to the bathing solution. The channel activity lasted for several seconds without long durations of desensi-
of reverse peptide Aβ42 resulted in a significant change in $P_o$ ($0.22 \pm 0.013$, $n = 16$, $P < 0.05$; Fig. 2B), but Aβ40 did not result in any significant decrease in $P_o$ ($0.37 \pm 0.028$, $n = 10$; Fig. 2C). Application of reverse peptide Aβ42-1 also did not decrease $P_o$ ($0.37 \pm 0.041$, $n = 9$; Fig. 2D).

Analyses of channel open and close times revealed that synaptosomal AMPA receptors showed three distinct close times (Fig. 3A) and two distinct open times with the short open time duration being about $1.0 \text{ ms}$. The long openings were several ms in duration (Fig. 3B). Application of Aβ1–40 did not cause any significant changes in open and closed time distributions (Figs. 3C and 3D). The effect of Aβ1–42 on open and closed time distributions was very profound. The shortest closed time remained without any significant changes before ($1.13 \pm 0.46 \text{ ms}$, $n = 11$; Fig. 3A) and after treatment with Aβ1–42 ($1.33 \pm 0.25 \text{ ms}$, $n = 11$; Fig. 3E). However, the longer closed times were significantly higher after Aβ1–42 treatment ($21.88 \pm 0.16 \text{ ms}$ and $237.37 \pm 0.11 \text{ ms}$, $n = 10$, $P < 0.05$; Fig. 3E) when compared to their control values before treatment ($5.05 \pm 0.82 \text{ ms}$ and $19.89 \pm 1.23 \text{ ms}$, $n = 11$, Fig. 3A). The longest closed times showed an increase by about 12-fold of the control value. The shorter open time remained unchanged significantly before ($0.82 \pm 0.31 \text{ ms}$, $n = 11$; Fig. 3B) and after treatment ($0.60 \pm 0.56 \text{ ms}$, $n = 11$; Fig. 3F). However, the longer open time showed a significant decrease, from $4.87 \pm 2.09 \text{ ms}$ to $1.73 \pm 0.55 \text{ ms}$ after treatment with Aβ1–42 ($n = 11$, $P < 0.05$; Figs. 3B and 3F). Application of Aβ42-1 did not significantly affect open times ($1.08 \pm 0.63 \text{ ms}$; $5.51 \pm 1.79 \text{ ms}$) or close times ($1.47 \pm 0.54 \text{ ms}$; $5.61 \pm 0.39 \text{ ms}$; $20.04 \pm 2.32 \text{ ms}$). In addition, single channel conductance (control, $28.3 \pm 2.07 \text{ ps}$) did not change significantly with neither application of Aβ1–42 ($26.1 \pm 1.84 \text{ ps}$), nor Aβ1–40 ($28.0 \pm 1.01 \text{ ps}$).

**DISCUSSION**

Synaptic dysfunction is the primary mechanism for the pathology of AD in its earliest stages (Selkoe, 2002). Aβ1–42 has been recently implicated in early stages of AD before substantial neuronal loss occurs because of their ability to accumulate faster than the formation of plaques (Bitan et al., 2003). It has been well established that Aβ1–42 disrupts hippocampal synaptic plasticity (Chang et al., 2006), and inhibits LTP in vivo (Walsh et al., 2002). Results of our study contribute to the current knowledge on synaptic glutamate receptor particularly AMPA receptor deregulation in early memory loss in AD. A previous study involving double knock-in mice carrying mutated human APP and presenilin-1 (PS1) genes determined that the decrease in AMPA receptor mEPSC amplitude corresponds to a dramatic rise in hippocampal Aβ1–42 levels consolidating the notion that Aβ1–42

Fig. 2. Open probability ($P_o$) of single channel currents of AMPA receptors in synaptosomes were attenuated by Aβ1–42 alone. (A) AMPA receptor single channel currents are evoked by addition of 290 nM of AMPA and voltage clamped at +94 mV. Current amplitude frequency histograms were fitted with Gaussian method and representative traces are shown next to the histogram. (B) Application of Aβ1–42 resulted in strong inhibition of $P_o$. (C) Application of Aβ1–40 did not result in significant reduction of $P_o$. (D) Application of reverse peptide Aβ42-1 did not alter the $P_o$. (E) Single channel currents were completely abolished by the specific AMPA receptor antagonist SYM 2206 (1 μM). Calibration: 5 pA, long traces are 1500 ms in duration, expanded segments are 100 ms in duration, holding potential. *$P < 0.05$, $n = 11$.
may be responsible for the reduced AMPA transmission in early stages of AD. Our study investigated the alterations in excitatory synaptic transmission mediated by AMPA receptors in the presence of Aβ1-40 or Aβ1-42. This was accomplished by using the whole cell patch clamp technique along with a unique technique involving reconstitution of synaptosomal AMPA receptors in artificial lipid bilayers (Vaithianathan et al., 2005). While the first approach provides information on the effect of Aβ peptides on synaptic currents at the cellular level, the second method is aimed at elucidating the effects of Aβ on single synaptic receptor properties that may contribute to modifications in synaptic currents.

Our results establish contrasting physiological effects of Aβ1-40 and Aβ1-42, which are in agreement with previous studies (Kuo et al., 1996; Raymond et al., 2003; Zou et al., 2003). Studies have also reported distinct differences in the structural properties of Aβ1-40 and Aβ1-42, and these differences are...
thought to play a major role in the contrasting biological effects of the two (Bitan et al., 2003). The longer peptide has two additional amino acids, isoleucine and alanine, and has the potency to form soluble oligomers and fibrils. At this time it is unknown which particular moiety of Aβ1–42 interacts with AMPA receptors. In our experiments, the shorter peptide, Aβ1–40 did not significantly alter the AMPA receptor mediated mEPSC amplitude or frequency. In addition, its effects on single channel properties were also negligible; thus, Aβ1–40 appears not to exert a modulatory effect on AMPA receptors. Several other studies have found that low levels of Aβ1–40 are in fact normally present in healthy nervous system tissue, implying a nonpathogenic physiological role (Busciglio et al., 1993; Haas et al., 1992; Masters et al., 1985).

Modulation of AMPA receptors by acute exposure to Aβ peptides implies that Aβ can interact with the receptors. In fact, Aβ peptides have been shown to bind with a variety of neuronal cell membrane proteins, including α7-nicotinic acetylcholine receptors (α7nAChRs) (Wang et al., 2000), NMDA receptors, and P75 neurotrophin (Verdier and Penke, 2004), indicating its potential to interact and modulate AMPA receptors. However, to our knowledge the in vitro effect of Aβ on single synaptic AMPA receptor channel properties has not been previously studied. We found that Aβ1–42 strongly decreased the single channel open probability and the mean open time of synaptic AMPA receptors. A reduction in these single channel parameters can contribute to a decrease in AMPA-mEPSC amplitudes and decay time, which is precisely what we observed.

Our data on the effects of Aβ1–42 on cultured slices showed a significant decrease in the frequency of mEPSC, indicating a possible reduction in presynaptic glutamate release. This is supported by a 40% reduction in presynaptic marker, synaptophysin, characteristic of postmortem human AD brains (Mann et al., 1996; Roher et al., 1993). Other in vitro studies have also confirmed an Aβ1–42 role in presynaptic dysfunction and subsequent impairment of vesicle release, yet Aβ1–40 has not shown a similar effect (Palmer et al., 1987; Satoh et al., 2001). This is in agreement with our observations that Aβ1–42, not Aβ1–40 modulates glutamatergic synaptic transmission.

Our results show that exogenously applied soluble Aβ1–42 can interact with AMPA receptors, and potently modulate their electrophysiological properties. Increased concentrations of this peptide in the functional synapses, along with its inhibitory effect on presynaptic release and postsynaptic receptors, can greatly reduce the efficiency of glutamatergic transmission. Given the intracellular effects of Aβ1–42 on receptor phosphorylation and on the postsynaptic proteins like PSD95 (Zhao et al., 2004; Almeida et al., 2005), it is evident the multifaceted actions of Aβ1–42 could result in a potent decline in hippocampal AMPA receptor mediated glutamatergic synaptic transmission. Our finding that Aβ1–42 directly modulates synaptic AMPA receptors provides new insight into the pathogenesis of AD. Furthermore, these results could help define possible strategies for a new drug design, aimed at restoring synaptic deterioration.

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REFERENCES


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