Brief Communications

Amyloid-β Impairs Synaptic Inhibition via $GABA_A$ Receptor Endocytosis

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Amyloid β (Aβ) is thought to play an important role in the pathogenesis of Alzheimer's disease. Aβ may exert its neurotoxic effects via multiple mechanisms and in particular through degradation of excitatory synaptic transmission associated with impaired synaptic plasticity. In contrast, much less is known about Aβ effects at inhibitory synapses. This study investigates the impact of acute Aβ1-42 application on GABAergic synaptic transmission in rat somatosensory cortex *in vitro*. Whole-cell voltage-clamp recordings were obtained from layer V pyramidal cells, and monosynaptic $GABA_A$ receptor-mediated IPSCs were elicited. Bath-applied Aβ (1 μM) depressed the IPSCs on average to 60% of control, whereas a reversed sequence control peptide was ineffective. Paired-pulse stimuli indicated a postsynaptic site of action. This was further corroborated by a decreased postsynaptic responsiveness to local puffs of the $GABA_A$ receptor agonist isoguvacine. The Aβ-induced IPSC decline could be prevented with intracellular applications of p4, a blocker of $GABA_A$ receptor internalization. It is concluded that Aβ weakens synaptic inhibition via downregulation of $GABA_A$ receptors.

Key words: **Alzheimer; amyloid-β; cortex; GABA; IPSP; plasticity**

Introduction

Alzheimer's disease is characterized by a steady cognitive decline and loss of memory function. A main pathophysiological agent is the protein β-amyloid (Aβ) that, although possibly playing a physiological role under normal conditions, gets transformed into a toxic substrate (Palop and Mucke, 2010). Aβ is known to increase Ca^{2+} influx into cells (Demuro et al., 2010) that may lead to hyperexcitability (Busche et al., 2008; Minkeviciene et al., 2009) and enhanced release of the neurotransmitter glutamate (Abramov et al., 2009). Both processes may interact in the subsequent removal of glutamatergic receptors from synapses (Hsieh et al., 2006). The loss of glutamate receptors is accompanied by an impairment of long-term potentiation, a long-lasting form of synaptic plasticity (Palop and Mucke, 2010; Walsh et al., 2002). It is believed that the decline in synaptic plasticity is responsible for the progressive loss of cognitive and memory functions in Alzheimer's patients (Selkoe, 2002). Although there is substantial evidence for an Aβ-associated pathophysiology at glutamatergic synapses, much less consistent data exist for GABA, the main inhibitory neurotransmitter in the forebrain. Early postmortem studies concluded that GABAergic cells were spared in Alzheimer's disease (for review, see Rissman et al., 2007). However, there is more recent evidence for differential upregulation and downregulation of particular $GABA_A$ receptor subunits in reconstituted human postmortem tissue of Alzheimer's patients, probably reflecting the coexistence of degenerative and compensatory processes (Limon et al., 2012). In animal models of Alzheimer's disease, tonic GABAergic inhibition was found to be upregulated in dentate granule cells of hippocampus (Wu et al., 2014). In contrast, phasic GABAergic synaptic transmission was found to be decreased (Busche et al., 2008), unaltered (Kamenetz et al., 2003), or enhanced (Palop et al., 2007). Part of these discrepancies may result from differences in the particular disease model investigated, the brain region examined, and/or experimental parameter assessed (e.g., morphological, neurochemical vs physiological) (Lanctôt et al., 2004). To better understand the role of synaptic inhibition in Alzheimer's disease, this study investigates the impact of Aβ on GABAergic synaptic transmission and describes an Aβ-mediated decline of IPSCs via $GABA_A$ receptor endocytosis.

Materials and Methods

Tissue preparation. All experimental procedures were approved by the Bioresources Committee, Trinity College Dublin, and licensed by the Department of Health and Children, Ireland, in accordance with European Communities Council Directive (86/609/EEC). Wistar rats of either sex (P21-P25) were kept on a 12 h light/dark cycle with food and water *ad libitum*. Rats were killed by decapitation, and the brains were quickly removed. Each hemisphere was glued onto a specimen platform slanted at 10°. Parasagittal slices of 300 μm thickness containing somatosensory cortex were prepared on a vibratome (Microm HM650V) in 4°C cold standard ACSF. The ACSF contained the following (in mM): 125 NaCl, 1.25 NaH_2PO_4, 25 $NaHCO_3$, 2.5 KCl, 1 $MgCl_2$, 2 $CaCl_2$, 10 glucose, pH 7.3, equilibrated with 5% CO_2/95% O_2. Slices were incubated in a submerged chamber at 34°C for 1 h and kept at room temperature thereafter.

Electrophysiology. Individual slices were transferred into a submerged recording chamber and superfused at a rate of 6 ml/min with ACSF warmed to 34°C. Whole-cell patch-clamp recordings were performed under visual control with an infrared differential interference contrast

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video microscope (Olympus BX51WI) (Stuart et al., 1993). Layer V of the somatosensory cortex was identified at low magnification (4×), and individual pyramidal cells were visualized with a 40× water-immersion objective. Patch pipettes were pulled on a DMZ universal puller (Zeitz Instruments) from thick-walled glass capillaries (Hilgenberg). Pipettes were filled with a filtered solution containing the following (in mM): 125 Cs-gluconate, 5 NaCl, 0.1 EGTA, 10 HEPES, 4 ATP, 0.4 GTP, pH 7.3 (osmolarity = 290 mosmol). Whole-cell currents were recorded in continuous single-electrode voltage-clamp mode (BVC-700A, Dagan) and digitized at 3 kHz (Digidata 1440A, Molecular Devices). A liquid junction potential of −10 mV was left uncorrected. IPSCs were evoked locally with constant current pulses (0.1–0.3 ms, 50–200 μA) via insulated bipolar nickel-chromium wires (Good Fellow) that were connected to an isolated pulse stimulator (A-M Systems). Agonist-evoked responses were generated by applying isoguvacine puffs (0.5 mM in ACSF, Picospritzer III, Parker) of 2–4 ms duration and 2–10 PSI amplitude through a wide focal patch pipette that was positioned in the neighborhood of the cells.

Chemicals. All drugs were stored as 1000× aliquots in distilled water and bath applied at final concentrations as indicated. Stock solutions of synthetic human β-amyloid 1-42 (shAβ1-42) and its reverse control 42-1 (Bachem) were prepared in 0.1% NH_4OH (Teplow, 2006) at a concentration of 0.2 mM and kept at −20°C. Leupeptin and bestatin were from Sigma-Aldrich. All other drugs were from Tocris Bioscience. Aliquots of the dynamin inhibitory peptide (p4, QVPSRPNRAP) were dissolved in water at a concentration of 0.9 mM and kept at −20°C. A control peptide was generated by denaturating aliquots of p4 at 100°C for 10 min. p4 or its control was added to the pipette solution at the concentrations indicated.

Data analysis. IPSC amplitudes were measured with 2 pairs of 1- to 3-ms-wide cursors for baseline and peak (pClamp 10, Molecular Devices). Paired stimuli were evoked at an interval of 50 ms, and the paired-pulse ratio was calculated as <IPSC2>/<IPSC1> (<> designates averages of 50 IPSC amplitudes). It was previously shown that calculating the paired-pulse ratio from averaged versus individual traces yields more accurate estimates (Kim and Alger, 2001). Baseline-subtracted, agonist-evoked responses were integrated to obtain an estimate of charge. Twenty consecutive amplitude or area values in control and Aβ were averaged and the ratio calculated to obtain an estimate of drug-induced changes. Data are presented as mean ± SEM, and *n* designates the number of cells. Statistical comparisons were done with the two-tailed, two-sample Student's *t* test.

Results

Aβ1-42 reduces GABAergic IPSCs

Layer V pyramidal cells were visually identified in the somatosensory cortex, and whole-cell patch-clamp recordings were established. To increase the electrochemical driving force for chloride, which had a Nernst equilibrium potential of −85 mV, individual neurons were voltage-clamped at 0 mV. Monosynaptic IPSCs were evoked focally with extracellular stimuli at 0.1–0.2 Hz after blocking ionotropic glutamatergic synaptic transmission with D-APV (50 μM) and DNQX (20 μM). QX314 (10 mM) was routinely added to the intracellular solution to block regenerative activity and $GABA_B$ receptors (Nathan et al., 1990). Evoked IPSCs in control had an average peak amplitude of 208 ± 39 pA ($n = 14$ cells). After recording a stable sequence of IPSCs in control, Aβ1-42 (1 μM) was added to the bath. Aβ application led to a decline of IPSC amplitudes to on average 61 ± 5% of control ($n = 14$ cells), which was statistically significant ($p < 0.0005$, paired *t* test) (Fig. 1*A*). In a subset of experiments, IPSCs were fully blocked by the selective antagonist bicuculline (10 μM) at the end of the recordings to verify that the IPSCs were exclusively mediated by $GABA_A$ receptors (e.g., see Fig. 4*A*). A similar series of experiments was subsequently undertaken with the control reverse sequence peptide Aβ42-1. Again, a stable series of IPSCs was recorded in normal ACSF. However, bath application of Aβ42-1 left IPSCs unaltered (Fig. 1*B*). Overall, the IPSC amplitudes were not significantly reduced by the control peptide to 93 ± 9% of control ($n = 5$, $p > 0.1$, paired *t* test), indicating that the observed depression of the IPSCs could be specifically attributed to Aβ1-42. Figure 1*C* shows a summary histogram of the net effects of Aβ1-42 and 42-1 on monosynaptic $GABA_A$ receptor-mediated IPSCs revealing a statistically significant difference between the two peptides ($p < 0.01$, unpaired *t* test).

Aβ1-42 acts postynaptically

At excitatory synapses, Aβ has been shown to affect neurotransmitter release as well as the number of neurotransmitter receptors in the postsynaptic membrane. A series of experiments was performed applying paired-pulse stimuli to determine the main site of action of Aβ at inhibitory synapses (Fig. 2*A*). Presynaptic $GABA_B$ receptors were routinely blocked in these experiments by adding 0.5 μM of the specific antagonist CGP52432 to the bath. Similar to previous paired-pulse experiments with $GABA_B$ receptors blocked (Pearce et al., 1995), the average paired-pulse ratio for IPSCs at 50 ms interstimulus interval showed a small depression of 0.88 ± 0.07. The paired-pulse ratio was not significantly altered by Aβ to 0.81 ± 0.07 ($n = 14$, $p > 0.1$, paired *t* test), indicating that the probability of GABA release is unlikely a main parameter affected by Aβ (Fig. 2*B*). To corroborate further a mainly postsynaptic site of Aβ action at inhibitory synapses, an additional set of recordings was performed by puffing the $GABA_A$ receptor agonist isoguvacine locally to neurons at an interpuff interval of 20 s (Fig. 3*A*). Glutamatergic synaptic transmission was again routinely blocked in these experiments by adding APV and DNQX to the bath. Repetitive isoguvacine puffs induced a series of stable transient outward currents in control that were reduced by Aβ and fully blocked by bicuculline (Fig. 3*A*). Overall, Aβ significantly reduced the total charge of the current from on average 516 ± 138 pC to 411 ± 143 pC ($n = 6$, $p < 0.05$, paired *t* test) (Fig. 3*B*). Together, the paired-pulse and isoguvacine data identify the postsynaptic membrane as the main target of Aβ actions in these experiments.

Aβ1-42 downregulates GABA receptors

Endocytosis and exocytosis of $GABA_A$ receptors are important mechanisms through which neurons regulate the strength of synaptic inhibition (Vithlani et al., 2011). In particular, $GABA_A$ receptors are known to be removed from the plasma membrane by clathrin-mediated endocytosis, a process that requires interactions between dynamin and amphiphysin (Kittler et al., 2000). To investigate whether Aβ affects $GABA_A$ receptor endocytosis, IPSCs were elicited with the dynamin inhibitory peptide p4 (50 μM) intracellularly applied via the patch pipette in combination with the protease inhibitors leupeptin (0.1 mM) and bestatin (0.1 mM) (Fig. 4) (Kittler et al., 2000). When p4 was allowed to diffuse into cells, IPSCs were no longer significantly reduced by Aβ to 85 ± 9% of control ($n = 9$, $p > 0.1$, paired *t* test) (Fig. 4*A*). To verify that this effect was indeed attributable to p4, a similar series of experiments was performed with a heat-inactivated control version of p4. When the control form of p4 was included in the patch pipette solution together with leupeptin and bestatin, IPSCs were again significantly reduced by Aβ to 45 ± 13% of control ($p < 0.05$, $n = 4$, paired *t* test) (Fig. 4*B*). Comparison of all recordings with p4 and its control showed a statistically significant difference ($p < 0.05$, unpaired *t* test) (Fig. 4*C*). Overall, these experiments indicate that Aβ affects inhibitory synapses through $GABA_A$ receptor endocytosis.

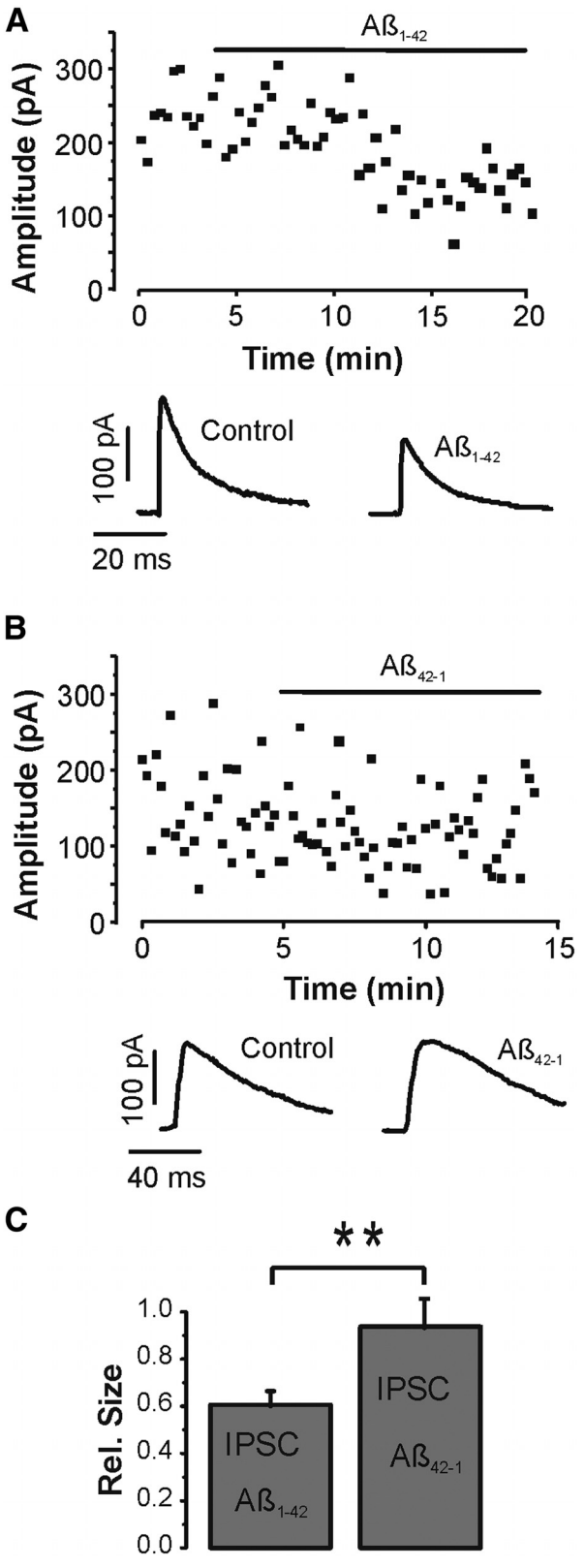

Figure 1. Aβ diminishes GABAergic synaptic transmission. ***A***, IPSC amplitude time course (■) and sample IPSCs (bottom) recorded in whole-cell voltage-clamp mode at 0 mV. Aβ (1 μM) was bath applied as indicated by the horizontal bar. There is pronounced reduction of the IPSCs after the peptide was added. The glutamate receptor antagonists DNQX (20 μM) and APV (50 μM) were present throughout the experiment. ***B***, Similar experiment to ***A*** with the reversed control peptide of Aβ. The control peptide had no significant effect on the IPSCs. ***C***, Summary histograms (mean ± SEM) of all experiments with the active ($n = 14$) and control ($n = 5$) sequence of Aβ indicating a statistically significant difference. $^{**}p < 0.01$ (unpaired *t* test).

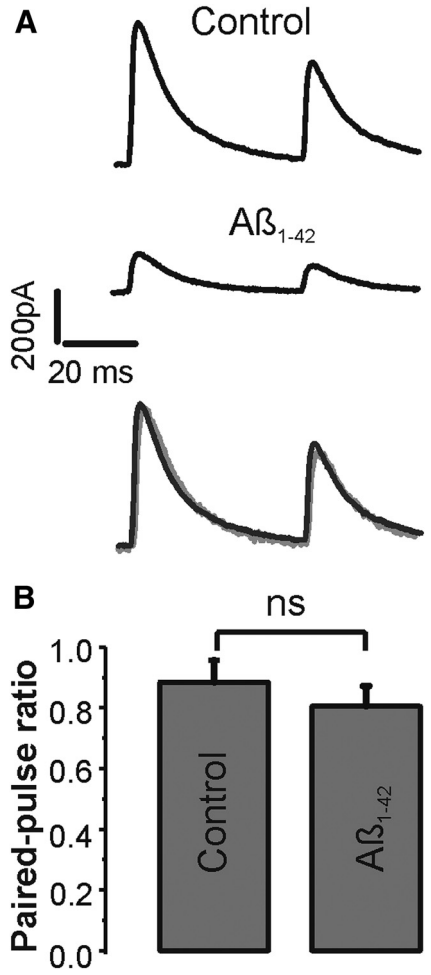

Figure 2. Short-term plasticity is unchanged by Aβ. ***A***, Paired-pulse IPSCs elicited at a 50 ms interval in control and Aβ (1 μM). Bottom, Overlay of normalized control and Aβ traces for comparison. DNQX (20 μM), APV (50 μM), and CGP52432 (0.5 μM) were present throughout the recordings. ***B***, Summary histograms (mean ± SEM) of all paired-pulse experiments in control and Aβ ($n = 14$) reveal no statistically significant difference. ns, Not significant ($p > 0.1$, paired *t* test).

Discussion

This study shows that Aβ, a main causative agent in the pathogenesis of Alzheimer's disease, directly interferes with synaptic inhibition in pyramidal cells of neocortex via downregulation of $GABA_A$ receptors. Controversial data exist on whether and to what degree Aβ affects synaptic inhibition in various experimental preparations. In acute applications, Aβ fragments 1-40 and 25-35 were shown to decrease agonist-evoked GABA responses in *Aplysia* neurons (Sawada and Ichinose, 1996). In contrast, GABA responses in acutely dissociated hippocampal neurons were potentiated by Aβ 25-35 and Aβ 31-35 (Zhang et al., 2009). This may indicate that the net effect of Aβ is fragment- and cell-type specific. In the present study, the Aβ 1-42 alloform was used because of its presence in Alzheimer's brains and its tendency to form oligomers, which are thought to be the main toxic agent in Alzheimer's disease. In line with the current findings, a comparable reduction of GABAergic inhibition was recently reported in the hippocampus under similar experimental conditions (Kurudenkandy et al., 2014). This indicates that acute Aβ effects on GABAergic synapses are not confined to neocortical areas but are also present in phylogenetically older parts of the brain. There is

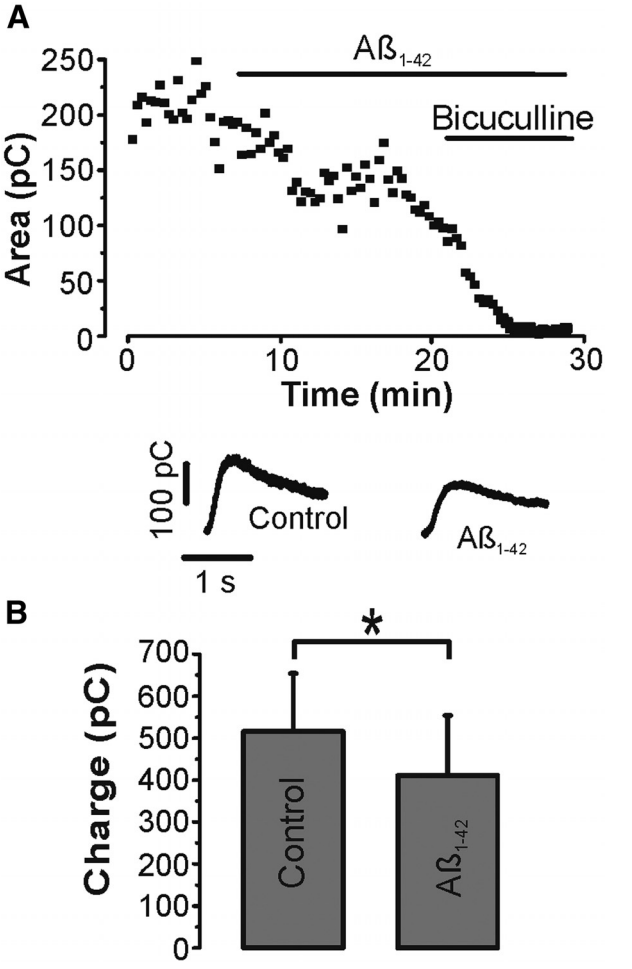

Figure 3. Aβ decreases agonist-evoked $GABA_A$ responses. ***A***, Time course (■) and sample traces of transient outward currents generated by brief puffs of 0.5 mM isoguvacine repeated every 20 s in control, Aβ (1 μM), and bicuculline (10 μM). ***B***, Summary histograms (mean ± SEM) of isoguvacine responses in Aβ versus control ($n = 6$) show a statistically significant difference. *$p < 0.05$ (paired *t* test).

limited agreement on the adequate concentration of Aβ for experimental Alzheimer's studies. The concentration of Aβ1-42 in the interstitial fluid of patients with Alzheimer's disease can be in the range of picomolar to low nanomolar but is thought to be significantly higher in the vicinity of senile plaques (Mucke and Selkoe, 2012). Low micromolar concentrations of Aβ that are widely used in *in vitro* studies may therefore be of pathophysiological relevance, even more so because the actual Aβ concentration in the slice may be considerably lower than in the superfusing bath (Waters, 2010).

There are experimental data supporting presynaptic and postsynaptic sites of Aβ action at excitatory synapses. The paired-pulse data from this study show a reduction in IPSCs without concomitant change in the paired-pulse ratio. This is usually taken as an indicator for a postsynaptic site of action, although the paired-pulse ratio may not be fully conclusive (Kim and Alger, 2001). However, the similar Aβ-induced reduction of agonist-evoked GABA responses and IPSCs renders a major presynaptic contribution to the observed decline unlikely. Nevertheless, a presynaptic influence may become apparent with different concentrations of Aβ and/or stimulation patterns as seen at excitatory synapses (Ting et al., 2007; Abramov et al., 2009). Adding to the complexity of amyloid effects on GABAergic synaptic trans-

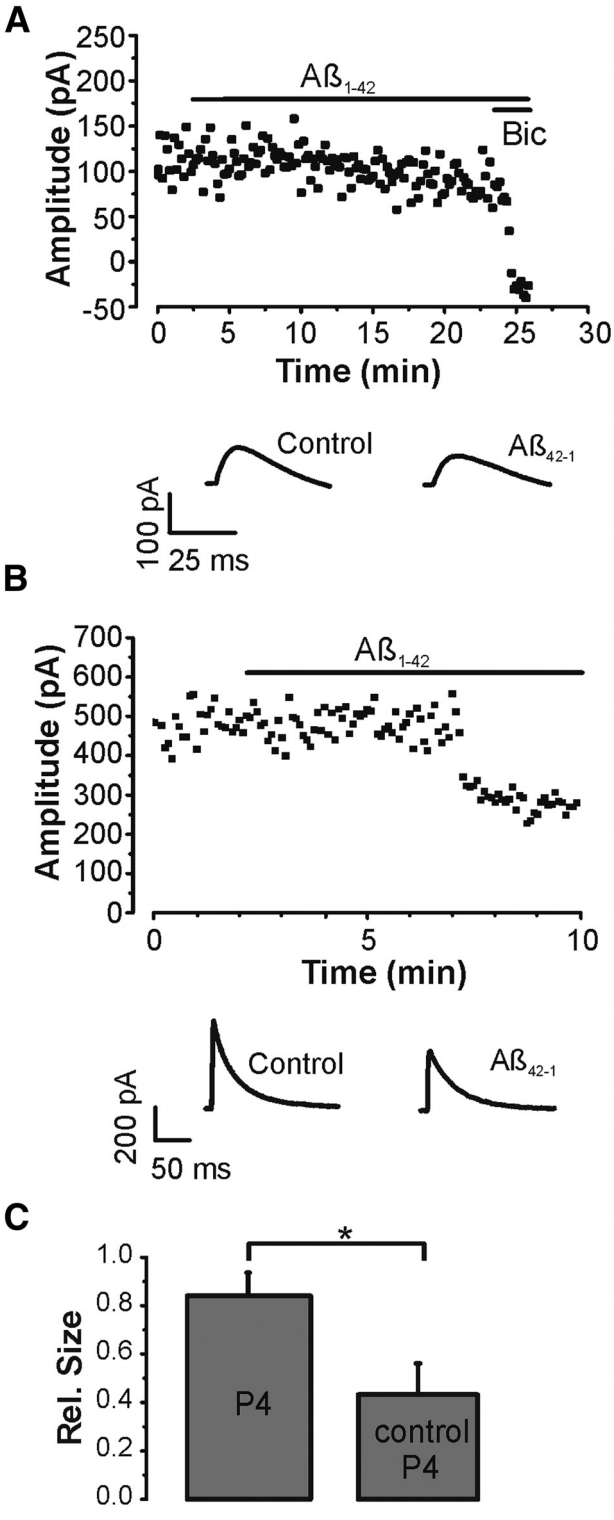

Figure 4. Aβ promotes $GABA_A$ receptor endocytosis. ***A***, IPSC amplitude time course (■) and sample IPSCs (bottom) in an experiment where 50 μM p4 was added to the patch pipette solution together with the protease inhibitors leupeptin (0.1 mM) and bestatin (0.1 mM). Aβ (1 μM) was bath applied as indicated by the horizontal bar. IPSCs were completely blocked by bicuculline (10 μM) toward the end of the experiment. DNQX (20 μM), APV (50 μM), and 0.5 μM CGP52432 were present throughout the recordings. ***B***, Amplitude time course (■) and sample IPSCs (bottom) in a similar recording with a control form of p4 applied intracellularly together with leupeptin (0.1 mM) and bestatin (0.1 mM). Aβ (1 μM) was added to the bath as indicated by the horizontal bar. DNQX (20 μM), APV (50 μM), and 0.5 μM CGP52432 were present throughout. ***C***, Summary histogram (mean ± SEM) of all experiments involving p4 ($n = 9$) and its control ($n = 4$) shows a statistically significant difference. *$p < 0.05$ (unpaired *t* test).

mission is the recent observation that the amyloid precursor protein itself can limit the amount of GABA released through direct protein-protein interactions (Yang et al., 2009). This suggests that presynaptic as well as postsynaptic processes may contribute synaptic impairment at inhibitory synapses in Alzheimer's disease.

The number of $GABA_A$ receptors on the cell surface is controlled by receptor trafficking involving exocytosis and endocytosis (Vithlani et al., 2011). The prevention of the Aβ-induced decline of IPSCs by p4, a peptide that inhibits the dynamin-mediated removal of $GABA_A$ receptors from the plasma membrane (Kittler et al., 2000), indicates that Aβ exerts its effect via receptor endocytosis. A similar mechanism has previously been shown to underlie the Aβ-induced decrease of glutamatergic synaptic transmission (Hsieh et al., 2006). Of note, no p4-related upregulation of IPSCs was seen in the present study, as originally reported by Kittler et al. (2000). However, the absence of a p4-induced increase of GABA receptors is in line with previous data from cortical pyramidal neurons (Kurotani et al., 2008), indicating that this phenomenon may be cell-type specific. The detailed signaling pathways between Aβ and GABA receptor endocytosis remain to be determined. Synaptic excitotoxicity is unlikely involved because ionotropic glutamate receptors were routinely blocked in the experiments. Similarly, a role for metabotropic neurotransmitters is unlikely as the intracellularly added Cs^+ and QX314 block several of their main effectors. Preliminary experiments with a high Ca^{2+} buffer did not prevent a decline of the IPSCs (data not shown), arguing against a role for Ca^{2+} triggered endocytosis. Direct interactions of Aβ with GABA receptors or Aβ-mediated intracellular signaling may provide alternative mechanisms to be tested. The current findings add to previous studies showing compromised $GABA_B$ receptor-dependent synaptic inhibition after Aβ application (Nava-Mesa et al., 2013). Therefore, Aβ appears to interfere with both ionotropic and metabotropic GABA responses. In addition, in animal models, nonsynaptic mechanisms have been reported through which inhibitory interneurons may be compromised (Verret et al., 2012). Thus, there is experimental evidence for the existence of multiple processes that could compromise inhibitory pathways in the etiology of Alzheimer's disease. An overall impairment of inhibitory circuits would be compatible with the occurrence of hyperexcitability that has been seen in animal models of Alzheimer's disease and Alzheimer's patients (Amatniek et al., 2006; Minkeviciene et al., 2009) and that may eventually lead to increased amyloid plaque formation (Bero et al., 2011).

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