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Aβ(25–35) and Aβ(1–40) act on different calcium channels in CA1 hippocampal neurons

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Abstract

The acute effects of β-amyloid (25–35) and (1–40) on high voltage activated calcium channels were compared in CA1 pyramidal cells of adult mouse hippocampal slices using the whole-cell patch-clamp recording. Bath application of oligomeric β-amyloid (25–35) reversibly increased the barium current (I_{Ba}) to 1.61 (normalized amplitude), while oligomeric β-amyloid (1–40) reversibly enhanced the I_{Ba} to 1.74. Reverse-sequence β-amyloid [(35–25) and (40–1)] had no effect. The effect of β-amyloid (25–35) was blocked by nifedipine, a selective antagonist of L-type calcium channels. In contrast, the effect of β-amyloid (1–40) was not blocked by nifedipine and I_{Ba} was enhanced to 4.96. It is concluded that these oligomeric peptides may act through different types of calcium channels and/or receptors. The toxicity of Aβ(25–35) implicates a potentiation of L-type calcium channels while the one of Aβ(1–40) is related to an increase of non-L-type calcium channels, which may involve an increase in transmitter release.

Keywords: β-Amyloid; Calcium channels; Hippocampus; Alzheimer

Alzheimer's disease is a neurodegenerative disorder that affects cognitive brain function of the brain. Pathological changes in Alzheimer's disease include the formation of amyloid plaques and neurofibrillar tangles and extensive neuronal loss, especially in the cortex and hippocampus [1,2]. Amyloid plaques, which accumulate extracellularly, are composed of aggregated β-amyloid peptides [3,4]. These 40–43 amino acid peptides are generated by alternate cleavage from the larger "amyloid precursor protein" [5,6]. Increased secretion of β-amyloid peptides (Aβ) has been associated with Alzheimer's disease [1] and it has been shown that in cell cultures Aβ in the micromolar range may be cytotoxic [7,8]. Aβ(25–35) is toxic in both the aggregated and soluble states [7]. Moreover, oligomeric Aβ(1–40) or Aβ(1–42) induces neuronal cell death in the nanomolar range [9,10]. Interestingly, Aβ oligomers were found to be naturally secreted and they inhibit long-term potentiation in the hippocampus [11]. Aβ peptides may be directly toxic to neurones in culture or potentiate neuronal vulnerability to excitatory neurotoxins (e.g., [12,13] and destabilize calcium homeostasis [13,14]. These effects may derive from the formation of ion channels within the cell membrane by Aβ, fostering direct leakage of calcium into cells [15,16]. Additional studies indicate a role for calcium channels in mediating Aβ actions on neurons, as Aβ induced neurodegeneration can be prevented by the application of L-type calcium channel blockers ([17,18] see however [19]) or Co^{2+}, a non-selective calcium channel blocker [18,20]. Electrophysiological studies in cultured cells have shown that a 24 h incubation with micromolar doses of aggregated Aβ(1–40) and Aβ(25–35) increased the L-type calcium channel activity [21,22], whereas in cerebellar granule cells and neocortical neurons a 24 h incubation with soluble Aβ(1–40) increased the non-L-type calcium channel activity [23,24]. The goal of the present experiments was to compare the acute effect on calcium channel activity of the oligomeric β-amyloid peptides, Aβ(25–35) and Aβ(1–40), in the nanomolar range, in CA1 adult mouse hippocampal cells. We find that the

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effect of Aβ(25–35) but not the effect of Aβ(1–40) was blocked by nifedipine, a selective blocker of L-type calcium channels.

Methods

SDS–PAGE. To determine whether the Aβ peptides were oligomeric or monomeric, we performed SDS–PAGE. Aliquot of each chromatographic fraction (20 μl) was mixed with Tris–HCl SDS sample buffer (10 μl) and boiled for 10 min, immediately prior electrophoresis (≈1 nmol/lane was electrophoresed; [25]) on 4–20% gradient acrylamide/bi-acrylamide gel (BioRad) at 125 V for 1 h. Proteins were visualized by silver staining. Image analysis was performed using Photomat (Microvision Instrument).

Slice preparation. High voltage activated calcium currents were whole-cell recorded from CA1 pyramidal cells in hippocampal slices according to previously published methods [26]. Briefly, hippocampal slices (300 μm thick) from 2- to 3-month-old mice were cut on a vibratome in cold (4 °C) sucrose saline containing (mM): 3 KCl, 7 $MgCl_2$, 1.25 NaH_2PO_4, 0.5 $CaCl_2$, 26 $NaHCO_3$, 252 sucrose, and 10 D-glucose. Slices were incubated in a warm (32 °C) oxygenated (95% O_2, 5% CO_2) normal saline (124 NaCl, 3 KCl, 1.15 $MgCl_2$, 1.25 NaH_2PO_4, 2 $CaCl_2$, 26 $NaHCO_3$, and 10 D-glucose) for 1 h before electrophysiological recordings. A slice was then transferred to the glass bottom of a recording chamber on an upright microscope and superfused with saline at 2 ml min^{-1}. All experiments were performed at room temperature (22 °C).

The whole-cell recording pipettes (2–5 MΩ) were tip-filled with (in mM): 135 CH_3SO_4Cs, 10 Hepes, 5 BAPTA, 5 NaCl, 0.5 $CaCl_2$, 1 $MgCl_2$, 4 Mg_2ATP, and 0.2 GTP (pH adjusted to 7.3 with CsOH, 280 mosm). The pipettes were then back-filled with an "ATP regenerating" solution (in mM): 100 CH_3SO_4Cs, 10 Hepes, 5 BAPTA, 5 NaCl, 0.5 $CaCl_2$, 1 $MgCl_2$, 4 Mg_2ATP, 0.2 GTP, 12.5 creatine-phosphate, and 25 U ml^{-1} creatine phosphokinase (pH adjusted to 7.3 with CsOH). The "ATP regenerating" solution was designed to minimize the run-down of the currents. These solutions were aliquoted and kept at −20 °C. An aliquot was used only for one experiment and fresh solutions were made every week. Barium was used as the external charge carrier and barium currents (I_{Ba}) were recorded in the presence of an extracellular recording solution, designed to maximize calcium conductances and inhibit other ionic currents. This solution contained (mM): 100 NaCl, 3 KCl, 1.15 $MgCl_2$, 2 $BaCl_2$, 20 TEA, 0.5 4-aminopyridine, 0.001 tetrodotoxin (TTX), 5 $CsCl_2$, 26 $NaHCO_3$, and 10 glucose.

Electrophysiology. CA1 cells lying in the pyramidal cell layer were identified by infrared microscopy. Membrane current was filtered at 1 kHz and recorded using an Axopatch-1D amplifier (Axon Instruments). The holding potential was set to −60 mV and the whole-cell configuration was obtained once a high-resistance seal (>1 GΩ) had been established. At least 70% of the series resistance (R_s) was compensated. R_s tended to increase during the experiments, although compensation was adjusted. The present results include only cells with an initial R_s not exceeding 15 MΩ and no more than 20% increase in R_s was tolerated.

Data were digitized and analyzed using Acquis1 software (CNRS, France). I_{Ba} was evoked by a 150 ms depolarizing step to 0 mV (from a holding potential of −60 mV), at 0.033 Hz. The amplitude was measured at the end of the depolarizing step (steady-state current) and plotted versus time. I_{Ba} was corrected for leakage by subtraction of an appropriately scaled current from a 20 mV hyperpolarizing step.

The current/voltage (I/V) relationship was obtained by stepping from a holding potential of −60 mV to test pulses varying from −80 to +60 mV (150 ms). The maximum I_{Ba} in our conditions was obtained at a test potential of 0 mV. I_{Ba} was normalized to the maximum current amplitude and plotted against the test potential (V_c).

The results are expressed as means ± SEM differences. Statistical analysis has been done using the Wilcoxon test. $p < 0.05$ was considered indicative of a statistically significant difference.

Drugs. Aβ(25–35) and Aβ(1–40) were purchased from Bachem. They were dissolved in distilled water at a concentration of 200 μM and aliquoted before freezing at −20 °C. The reverse sequences (Aβ(35–25) and Aβ(40–1)) obtained from Bachem were prepared in the same way. During the experiment, Aβ was dissolved in saline at the concentration of 200 nM. Because of lot-to-lot variability, each new batch of Aβ was tested on the barium current before use. Nifedipine (Sigma) was dissolved in DMSO. The final concentration of DMSO was 0.3% and this concentration when applied alone (data not shown) did not affect I_{Ba} amplitude. TTX was obtained from Latoxan.

Results

SDS–PAGE analysis performed on the 200 μM stock solution revealed that Aβ(1–40) and Aβ(25–35) were oligomeric (4–6 mers for Aβ(1–40) and 6–8 mers for Aβ(25–35). Moreover DMSO, the solvent used in the nifedipine experiments, when added to the stock solution at the concentration of 5‰ (a dilution factor five times superior to that used in the experiment) did not change the oligomeric structure of the Aβ peptides (data not shown).

Aβ increased barium current in slices

Depolarizing cells to +20 mV from a holding potential of −60 mV evoked an inward I_{Ba}, which resulted mainly from the activation of high voltage activated calcium channels. Two separate batches of each Aβ peptide were used in independent experiments and similar results were obtained. Data from both batches were then pooled. No variation in the holding current and input resistance was observed ($p < 0.02$). Regression fits of the data for each cell gave a mean resting conductance of 5.70 ± 0.01 nS for control cells ($n = 56$) and 5.15 ± 0.02 nS for Aβ treated cells ($n = 53$).

Bath application of Aβ(25–35) (200 nM) caused an increase in the amplitude of I_{Ba} evoked at +20 mV in 6 out of 10 cells (Fig. 1). This increase (1.61 ± 0.03, $p = 0.036$, $n = 6$) reversed upon the drug wash-out. However, the increase in I_{Ba} developed slowly and 20 min of bath application was necessary before reaching a steady state, an effect which may be attributed to the slow penetration of Aβ in the slice or into the cells. Aβ(1–40) (200 nM) also reversibly increased I_{Ba} evoked at +20 mV (Fig. 2). This increase was observed for 6 of 11 cells and reached 1.74 ± 0.06 ($p = 0.032$, $n = 6$). The activation curves (Figs. 1 and 2) show that Aβ(25–35) and Aβ(1–40) caused an apparent voltage-dependent increase in I_{Ba}, with an enhancement of I_{Ba} at the test potentials between 0 and +30 mV. The reverse sequences of Aβ (Aβ(35–25), $n = 5$ and Aβ(40–1), $n = 5$) had no effect on I_{Ba} amplitude (data not shown).

Nifedipine blocked the effect of Aβ(25–35) but not the effect of Aβ(1–40)

Nifedipine, a selective blocker of L-type calcium channels, reduced the I_{Ba} amplitude by 20 ± 2% ($n = 22$,

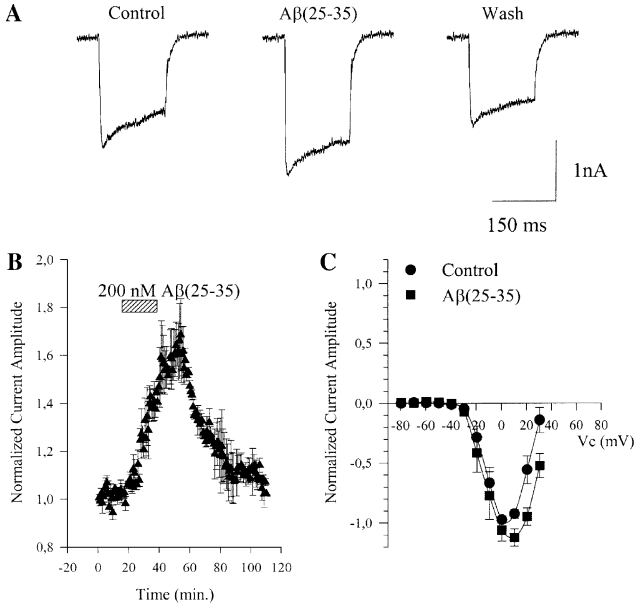

Fig. 1. Effect of Aβ(25–35) on I_{Ba} amplitude. (A) Individual I_{Ba} traces elicited by a 150 ms depolarizing step to 20 mV from a holding potential of −60 mV before, during, and after a 20 min bath exposure to 200 nM Aβ(25–35). The traces shown were obtained from the same cell. Tail currents were truncated, since we were interested only in the steady-state current. (B) Time course of the potentiation by Aβ(25–35) of I_{Ba} amplitude elicited by a depolarizing step to 20 mV. Amplitudes were normalized relative to the 10 min control period, prior to drug application. (C) Current/voltage (I/V) relationships obtained before (filled circles) at the end (filled squares) of exposure to Aβ(25–35).

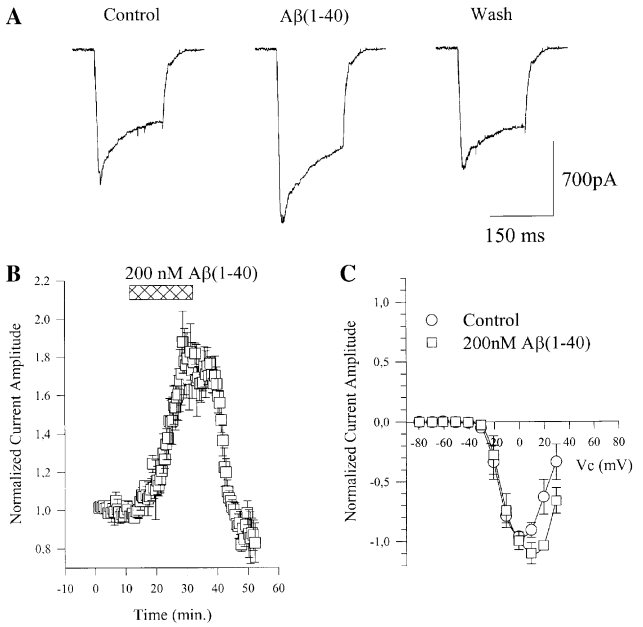

Fig. 2. Effect of Aβ(1–40) on I_{Ba} amplitude. (A) Individual I_{Ba} traces elicited by a 150 ms depolarizing step to 20 mV from a holding potential of −60 mV before, during, and after a 20 min bath exposure to 200 nM Aβ(1–40). Traces shown are from the same cell. (B) Time course of the potentiation by Aβ(1–40) of I_{Ba} amplitude elicited by a depolarizing step to 20 mV. Amplitudes were normalized relative to the 10 min control period, prior to the drug application. (C) I/V relationships obtained before (open circles) and at the end (open squares) of exposure to Aβ(1–40).

$p < 0.01$, Figs. 3 and 4). In the presence of 10 μM nifedipine, Aβ(25–35) failed to increase the I_{Ba} amplitude (Fig. 3). In contrast, Aβ(1–40) in the presence of nifedipine caused a large increase in I_{Ba} evoked at +20 mV (Fig. 4, 4.96 ± 0.03, $p = 0.03$) in 8 out of 16 cells. However, this enhancement did not reverse upon Aβ(1–40) wash-out. The activation curve (Fig. 3) shows that Aβ(25–35) in the presence of nifedipine did not increase I_{Ba}. On the contrary, Aβ(1–40) enhanced I_{Ba} at the test potentials between 0 and +30 mV (Fig. 4).

Discussion

The main finding of this paper is that adult CA1 hippocampal cells acutely exposed to nanomolar doses of Aβ peptides (25–35) or (1–40) exhibit an increase in the activity of different calcium channel types. In contrast to previous works [21,23,24,27,28], we have tested the Aβ peptides in its oligomeric form, a state of aggregation, which precedes the formation of fibrillar Aβ and plaques. An interesting issue, since the best pathological correlate of dementia is loss of synaptic terminals, which correlate poorly with amyloid load (see [29], for review). Our findings agree with previous work on cultured neurons either incubated with Aβ peptides in the micromolar range for 24 h [21,23,24] or acutely exposed to 1 μM Aβ(1–40) [27]. The fact that the cell input conductance did not vary and the absence of increased linear leak current excluded changes in the activity of non-calcium channels, or insertion of non-selective cation channels into the cell membrane, as it has been proposed [15]. However, a zinc-sensitive calcium entry through the calcium channels cannot be excluded [28].

In agreement with previous work [21,23], this increase in I_{Ba} appears voltage-dependent, the increase being obvious only at potentials more positive than 0 mV. These effects could be attributed to electrostatic interaction of Aβ peptide with the membrane [30] or a decrease in membrane fluidity [31]. The observation that not every cell exhibited an increase to Aβ peptides suggests that either not every cell was sensitive to Aβ or those sensitive to one of the peptides (e.g., Aβ(25–35)) were not affected by the other (e.g., Aβ(1–40)). Interestingly, it has been shown that Aβ induces the phosphorylation of calcium channels [22] and an involvement of Go protein has been proposed ([32], see however [12]), suggesting the activation of an unknown receptor.

We also show that the Aβ(25–35) effect on calcium channels was blocked by nifedipine, a selective blocker of L-type calcium channels, suggesting Aβ(25–35) increased the L-type calcium channels. In contrast to

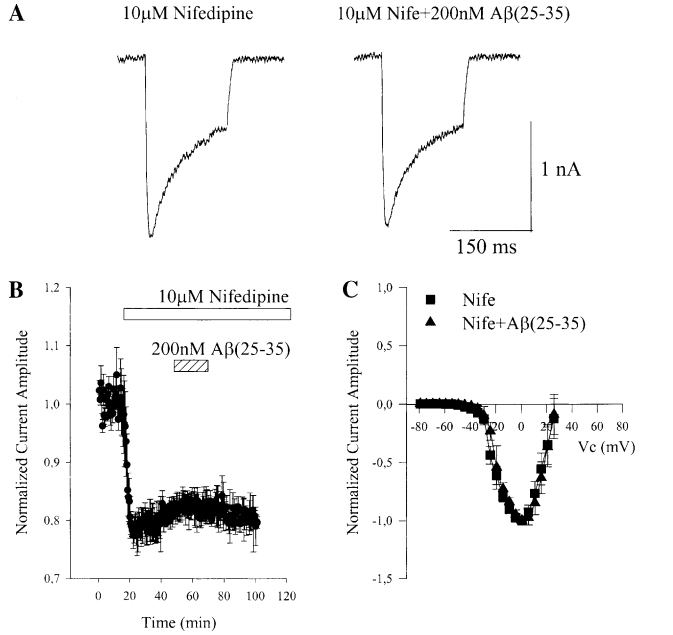

Fig. 3. Effect of Aβ(25–35) on I_{Ba} amplitude after the blockage of L-type calcium channels by 10 μM nifedipine. (A) Individual I_{Ba} traces elicited by a 150 ms depolarizing step to 20 mV from a holding potential of −60 mV during exposure to 10 μM nifedipine and after a 20 min bath exposure to 200 nM Aβ(25–35) plus 10 μM nifedipine. Traces are from the same cell. (B) Time course of the effect of nifedipine and of bath exposure to 200 nM Aβ(25–35) under nifedipine on I_{Ba} amplitude elicited by step depolarization to 20 mV. (C) Current/voltage (I/V) relationships obtained with 10 μM nifedipine (filled squares) and during exposure to 200 nM Aβ(25–35) plus 10 μM nifedipine (filled triangles).

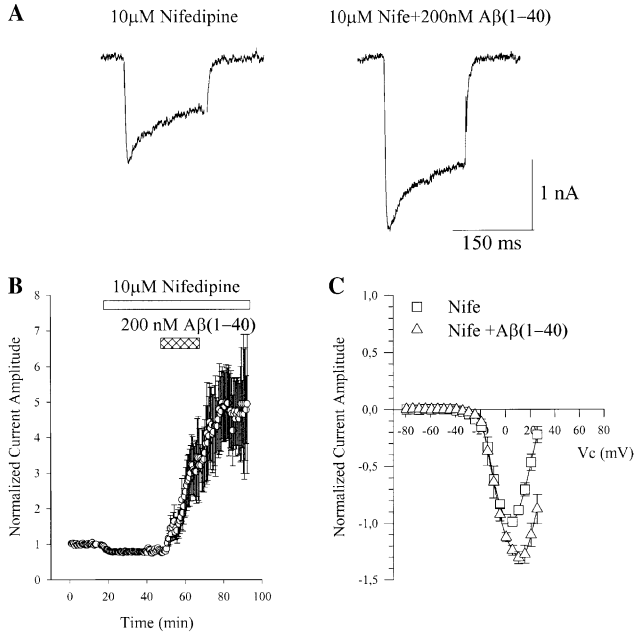

Fig. 4. Effect of Aβ(1–40) on I_{Ba} amplitude after the blockage of L-type calcium channels by 10 μM nifedipine. (A) Individual I_{Ba} traces elicited by a 150 ms depolarizing step to 20 mV from a holding potential of −60 mV with 10 μM nifedipine and after a 20 min bath exposure to 200 nM Aβ(1–40) plus 10 μM nifedipine. Traces are obtained from the same cell. (B) Time course of the effect of nifedipine and of 200 nM Aβ(1–40) plus nifedipine on I_{Ba} amplitude elicited by step depolarization to 20 mV. (C) I/V relationships obtained with 10 μM nifedipine (open squares) and after exposure to Aβ(1–40) plus 10 μM nifedipine (open triangles).

Aβ(25–35), the Aβ(1–40) effect was significantly increased by nifedipine, suggesting that Aβ(1–40) acts on non-L-type calcium channels. It is thus possible that Aβ(1–40) and Aβ(25–35) act through different types of receptors. Interestingly, it has been shown that incubation of cerebellar granule cells with soluble Aβ(1–40) increased the N-type calcium channel activity [23] and the N- and P-type calcium channel activity but not the L-type calcium channel activity in neocortical neurons [24]. However, incubation of neuroblastoma cells either with aggregated Aβ(1–40) or Aβ(25–35) induces the phosphorylation of L-type calcium channels [22], suggesting that the increase in L-type channel activity may depend on cell type and the aggregation state of Aβ peptides. The toxicity of Aβ, which is particularly attributed to the peptide (25–35) [8,13], is blocked by L-type calcium channel blockers [18], see however [17,19]. Our results raise the possibility that Aβ(1–40) toxicity would be mediated by an increase in transmitter release [12,13,33,34], since non-L-type calcium channels are involved in transmitter release.

In summary, these results show that in adult CA1 hippocampal pyramidal cells, oligomeric Aβ(25–35) and Aβ(1–40) acutely increase in the nanomolar concentration for different types of calcium channel activity. The toxic fragment, Aβ(25–35), increases the L-type calcium channel activity while Aβ(1–40) increases the non-L-type calcium channels. These data suggest that the mechanism of the destabilization of calcium homeostasis may be different for the two peptides, an action, which could be mediated through different types of receptors.

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