Cell Mol Neurobiol (2012) 32:219–226
DOI 10.1007/s10571-011-9751-9

ORIGINAL RESEARCH

Donepezil in a Narrow Concentration Range Augments Control and Impaired by Beta-Amyloid Peptide Hippocampal LTP in NMDAR-Independent Manner

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Received: 12 May 2011 / Accepted: 18 August 2011 / Published online: 4 October 2011
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Abstract Acetylcholinesterase (AChE) inhibitor donepezil is widely used for the treatment of Alzheimer's disease (AD). The mechanisms of therapeutic effects of the drug are not well understood. The ability of donepezil to reverse a known pathogenic effect of β-amyloid peptide (Abeta), namely, the impairment of hippocampal long-term potentiation (LTP), was not studied yet. The goal of the present study was to study the influence of donepezil in 0.1–10 μM concentrations on control and Abeta-impaired hippocampal LTP. Possible involvement of *N*-methyl-D-aspartate receptors (NMDARs) into mechanisms of donepezil action was also studied. LTP of population spike (PS) was studied in the CA1 region of rat hippocampal slices. Change of LTP by donepezil treatment had a bell-shaped dose–response curve. The drug in concentrations of 0.1 and 1 μM did not change LTP while in concentration of 0.5 μM significantly increased it, and in concentration of 5 and 10 μM suppressed LTP partially or completely. Abeta (200 nM) markedly suppressed LTP. Addition of 0.1, 0.5 or 1 μM donepezil to Abeta solution caused a restoration of LTP. *N*-methyl-D-aspartate (NMDA) currents were studied in acutely isolated pyramidal neurons from CA1 region of rat hippocampus. Neither Abeta, nor 0.5 μM donepezil were found to change NMDA currents, while 10 μM donepezil rapidly and reversibly depressed it. Results suggest that donepezil augments control and impaired by Abeta hippocampal LTP in NMDAR-independent manner. In general, our findings extend the understanding of mechanisms of therapeutic action of donepezil, especially at an early stage of AD, and maybe taken into account while considering the possibility of donepezil overdose.

Keywords Donepezil · β-Amyloid peptide · Hippocampus · LTP · NMDA current

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Introduction

Beta-amyloid peptide (Abeta) cascade hypothesis is widely used for explanation of Alzheimer's disease (AD) pathogenesis (Adlard et al. 2009). This hypothesis implies that soluble, non-fibrillar assembly forms of Abeta, maybe responsible for some of the pathological alterations underlying memory impairment in AD (Walsh and Selkoe 2007). Soluble Abeta oligomers have been demonstrated to induce disruption of synaptic plasticity that may underlie early symptoms of AD (Lesne et al. 2006). Consistently, some reports demonstrated that low concentrations of Abeta oligomer impaired long-term potentiation (LTP), a well-studied form of synaptic plasticity (Chen et al. 2002; Nomura et al. 2005; Ye and Qiao 1999). Search for drugs able to cope synaptic disfunctions induced by Abeta is an actual problem.

Donepezil hydrochloride is the most prescribed drug for treatment of AD (Relkin 2007). The main mechanism of its action on memory and cognition is presumed to be the inhibition of acetylcholinesterase (AChE) in the brain. The compound, however, may have pharmacological properties other than AChE inhibition. It has been demonstrated that different types of receptors: *N*-methyl-D-aspartate (NMDA) (Moriguchi et al. 2005), σ1 (Meunier et al. 2006), and α4nACh (Akaike et al. 2010), are the potential sites of interaction for donepezil that may contribute to its therapeutic effects. Donepezil has been described to protect

neurons against neurodegeneration induced by Abeta (Arias et al. 2005; Kimura et al. 2005). The ability of donepezil to reverse the impairment of hippocampal LTP induced by Abeta was not studied yet.

The goal of the present study was to study the influence of donepezil in 0.1–10 μM concentrations on control LTP in Schaffer collaterals—CA1 pyramidal cells in hippocampus as well as its ability to antagonize the suppressive effect of Abeta (1–42) on this form of synaptic plasticity. This study is further development of our previous study where donepezil was studied in 1 μM concentration only (Kapai et al. 2010). The investigations of influence of other AChE inhibitors on LTP in hippocampus demonstrated that galantamine, tacrine, and physostigmine enhance it (Moriguchi et al. 2009; Welsby et al. 2009), while (−)hyperzine A was found to cause no change in control LTP, but to offset the suppressive effect of Abeta (Ye and Qiao 1999).

Previously, the changes in hippocampal LTP induced by Abeta were determined from the changes in amplitude of population spike (PS) (Ye and Qiao 1999), the slope of the field excitatory postsynaptic potential (fEPSP) (Chen et al. 2002), or excitatory postsynaptic current (Nomura et al. 2005). In our study, we decided to record PS because it reflects both synaptic and non-synaptic events occurring during LTP. Recent data shows that besides synapse-specific changes, many additional electrophysiological components of neurons undergo use-dependent long-term plasticity, for example, voltage-gated ion channels (for review see, Debanne and Poo 2010).

N-methyl-D-aspartate receptors (NMDARs) were found to play central role in the induction of LTP in hippocampus (Chittajallu et al. 1998). The role of NMDRs in the mechanism(s) of Abeta-induced impairment of LTP as well as in the mechanism(s) of therapeutic action of donepezil is discussed in the literature. Recent studies have demonstrated that Abeta can cause loss of surface NMDARs (Snyder et al. 2005; Lacor et al. 2007; Dewachter et al. 2009). Electrophysiological investigations show that Abeta can decrease (Snyder et al. 2005; Chen et al. 2002; Raymond et al. 2003), increase (Wu et al. 1995; Molnár et al. 2004) or not change (Nomura et al. 2005) NMDAR-mediated responses. These various findings suggest that the effects of Abeta on NMDARs impair synaptic plasticity, but the detailed mechanism remains unknown. As for donepezil, this drug was shown to cause different effects, both augmenting and weakening, on NMDA-induced current in different rat cortical neurons in culture (Moriguchi et al. 2005). In the present study, we studied the effects of Abeta and donepezil on NMDA current in isolated pyramidal neurons of rat hippocampus in the same concentrations and duration of treatment as used in our LTP experiments.

Methods

Male Wistar rats (3–4 weeks old) were anesthetized with halothane and decapitated. Four-hundred-micrometer thick hippocampal slices were maintained for at least 2 h in slice chamber where artificial cerebrospinal fluid (ACSF) (29–30°C) was constantly replaced at a rate of 1.5 ml/min. This solution was oxygenated with 95% O_2 + 5% CO_2 and contained (in mM): 124 NaCl, 3 KCl, 2.5 $CaCl_2$, 1.25 Na_2HPO_4, 2.5 $MgSO_4$, 26 $NaHCO_3$, and 10 D-glucose. Extracellular recordings were made from the pyramidal layer of the CA1 region using glass micropipettes filled with 1.5 M NaCl. To elicit synaptic responses, Schaffer collateral/commissural afferents in stratum radiatum were stimulated through bipolar glass electrodes filled with a perfusion medium. Single pulses (0.066 Hz, 0.1 ms) ranging from subthreshold to supramaximal were used to obtain input–output curves (stimulus intensity vs. PS amplitude). The intensity of pulses used in experiments was adjusted so that evoked responses with amplitude of approximately half of maximum value. LTP was induced using one train of high-frequency stimulation (HFS) (100 Hz, 1 s). The amount of LTP was quantified as the percentage change in PS amplitude 30 min after the HFS by taking the average value of initial PSs at the first 2 min as the 100%. Drugs were added to the perfusate starting 15 min before and ending 5 min after the tetanus.

A solution containing Abeta (1–42) (Sigma) was prepared as described in the literature (Chen et al. 2002; Ye and Qiao 1999). Abeta was dissolved in distilled water to make stock solution, which was divided into small aliquots and flash frozen at −20°C. This process yields soluble monomers of Abeta (Nichols et al. 2005). Stock solution was diluted to desired final concentrations in ACSF immediately before application in each experiment. Samples of applied peptide solution were taken during the experiments and visually inspected under a phase-contrast microscope (×400) for the presence of fibrillar or sheetlike aggregates as described (Pike et al. 1995). No evident aggregates were observed in samples inspected. Donepezil solution was prepared by dissolving a tablet of Aricept (Pfizer) containing 5 mg of donepezil hydrochloride in distillated water. Donepezil solution was stored as 1 mM stock at 4°C and was freshly dissolved in ACSF for each experiment.

NMDA currents were recorded in pyramidal neurons acutely isolated from CA1 region of hippocampal slices as described in detail elsewhere (Vorobjev 1991). Briefly, Wistar rats (11–14 days old) were decapitated, slices 200–500 μm thick were cut with a razor blade and incubated at room temperature for at least 2 h. The incubation solution consisted of (in mM): 124 NaC1, 3 KC1, 2 $CaCI_2$, 2 $MgSO_4$, 25 $NaHCO_3$, 1.3 NaH2PO_4, 10 D-glucose, and

pH 7.4. The saline was continuously stirred and bubbled with carbogen (95% 0_2 + 5% CO_2). Neurons were dissociated by a vibrating fused glass pipette with a spheric tip. The dissociation procedure was carried out in the following saline (in mM): 140 NaC1, 3 KC1, 5 $CaCI_2$, 5 $MgCl_2$, 10 D-glucose, 10 HEPES hemisodium, and pH 7.4. Voltage-clamp recording was obtained using the whole-cell configuration of the patch-clamp technique (Hamill et al. 1981). Patch pipettes had resistances of 2–3 MΩ and were filled with (in mM): 40 CsF, 100 $CsCl_2$, 0.1 $CaCl_2$, 1 EGTA, 3 $MgCl_2$, 4 NaATP, 0.2 NaGTP, 5 HEPES, 0.2 IBMX, and pH 7.3. Experiments were performed at room temperature using a List EPC-7 patch-clamp amplifier. Recording was performed in Mg^{2+}-free bath solution of the following composition (in mM): 140 NaC1, 3 KC1, 3 $CaCI_2$, 10 D-glucose, 10 HEPES hemisodium, 0.02 picrotoxin, pH 7.4. Abeta and donepezil were prepared in the same way as for LTP experiments and were added to the bath solution. The speed of perfusion was 0.6 ml/min. L-Aspartic acid and glycine (Sigma) were dissolved in bath solution, which in this case contained 1 mM $CaCl_2$. NMDA currents were activated by L-aspartic acid (50 μM) and glycine (5 μM) (Curras and Dingledine 1992) applied for 1 s with 1 min intervals. These substances were applied through glass capillary, 0.1 mm in diameter, which could be rapidly displaced laterally under control by home-made software (Vorobjev et al. 1996). The holding potential was maintained at −70 mV. Data were collected with home-made software and stored on a computer disk.

Student's unpaired two-tailed *t*-test was used for statistical analysis. Group data is presented as mean ± SEM.

Results

High-frequency tetanus of the Schaffer/commissural afferents evoked LTP of PS in the CA1 region of the hippocampus (Fig. 1). In the control group, the PS amplitude reached 152.1 ± 10.0% ($n = 11$) at 30 min post tetanus. The AChE inhibitor donepezil in concentration of 0.1–10 μM had no effect on the baseline of PS but changed the LTP with a bell-shaped dose–response curve. Figure 1 shows the time course of changes in PS amplitude after tetanus when different concentrations of donepezil (0.1, 0.5, 1, 2, 5, and 10 μM) were applied. Starting concentration of donepezil (0.1 μM) did not have a significant effect on LTP: amplitude of PS 30 min post tetanus was 163.5 ± 10.1% ($n = 4$). Augmentation of donepezil concentration to 0.5 μM led to significant increase of LTP (194.4 ± 16.7%, $n = 5$, $P < 0.05$). Further increase of donepezil concentration (1 μM) resulted in return of LTP to initial level (163.9 ± 11.1%, $n = 5$), while higher concentrations (2, 5 and 10 μM) suppressed LTP (127.2 ± 10.8%, $n = 5$; 106.8 ± 9.3%, $n = 5$, $P < 0.05$; 97.1 ± 5.5%, $n = 4$, $P < 0.01$, correspondingly).

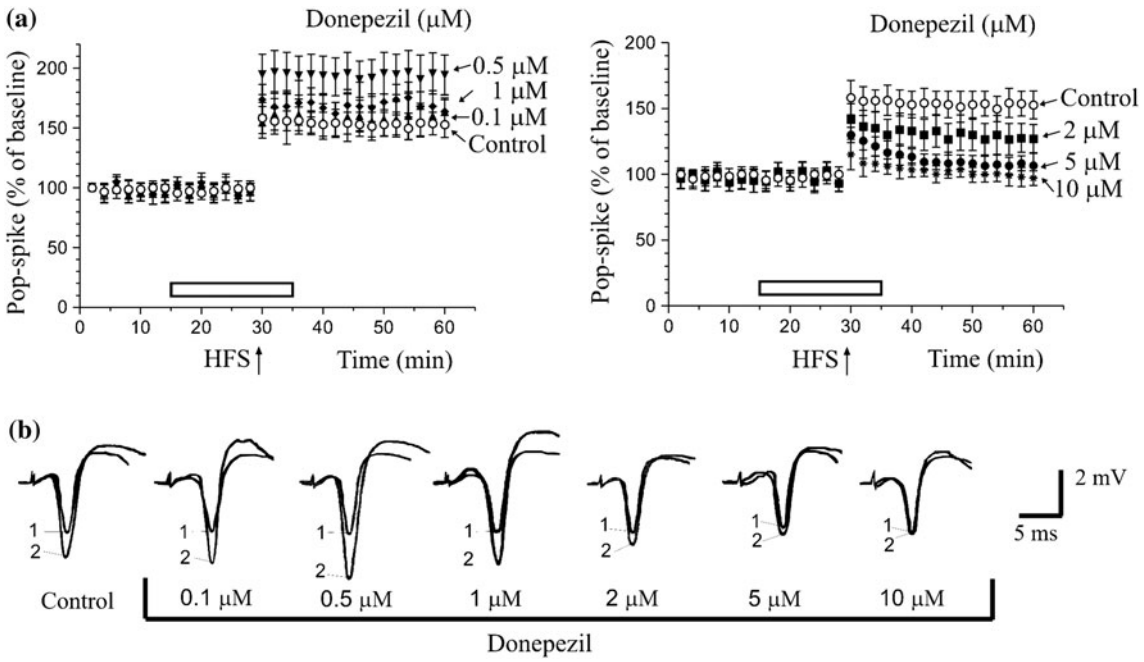

Fig. 1 Effects of donepezil on the tetanus-induced LTP of PS in the hippocampal CA1 region. **a** Time courses of LTP and the effects of 0.1–1 μM donepezil (*left side*) and 2–10 μM donepezil (*right side*). Each point is the mean ± SEM of normalized PS amplitude. *Arrows* indicate tetanus application and the *empty bars*—the duration of the drug perfusion. **b** Example of traces of PS before (*1*) and 30 min after tetanus (*2*) from untreated slices (control) or slices treated with different concentration of donepezil

Abeta (200 nM) did not influence PS evoked by single stimuli but completely blocked LTP: PS amplitude 30 min after tetanus was 81.9 ± 14.1 ($n = 7$, $P < 0.005$) as compared with the control group. However, this suppression could be markedly prevented when low concentrations of donepezil (0.1, 0.5 or 1 μM) were co-administered with Abeta. An addition of donepezil to Abeta solution caused the restoration of LTP magnitude 30 min post tetanus to 132.8 ± 13.9% ($n = 4$, $P < 0.05$) for 0.1 μM, 183.0 ± 17.9% ($n = 6$, $P < 0.005$) for 0.5 μM, and 136.4 ± 10.7% ($n = 5$, $P < 0.05$) for 1 μM of the drug (Fig. 2). The meanings of "P" in this series of experiments were estimated as compared with those in experiments where slices were treated with Abeta alone.

Figure 3 combines the results of all four series of experiments: control (no treatment), treatment with donepezil, with Abeta, and with Abeta plus donepezil. One can see that donepezil in therapeutically relevant concentrations can rise control LTP and restore LTP impaired by Abeta.

A tablet of Aricept besides donepezil hydrochloride contains the inert filling material, both soluble and insoluble. The insoluble ingredients (corn starch, microcrystalline cellulose, magnesium stearate, and talk) were filtered out. The main soluble ingredient of the inert filling material was lactose. We have calculated that in solution containing 0.5 and 10 μM donepezil the concentration of lactose was about 5 and 100 μM, accordingly. We studied the influence of 5 and 100 μM lactose (ChemMed, Russia) on hippocampal LTP in the absence and in the presence of Abeta, and found no noticeable effects (not shown). We could not find any description of lactose influence on LTP in the literature. At the same time, fucose and fucosyllactose were described to enhance LTP (Matthies et al. 1996). Our control experiments with lactose allow to conclude that all effects on LTP mentioned above are caused by donepezil.

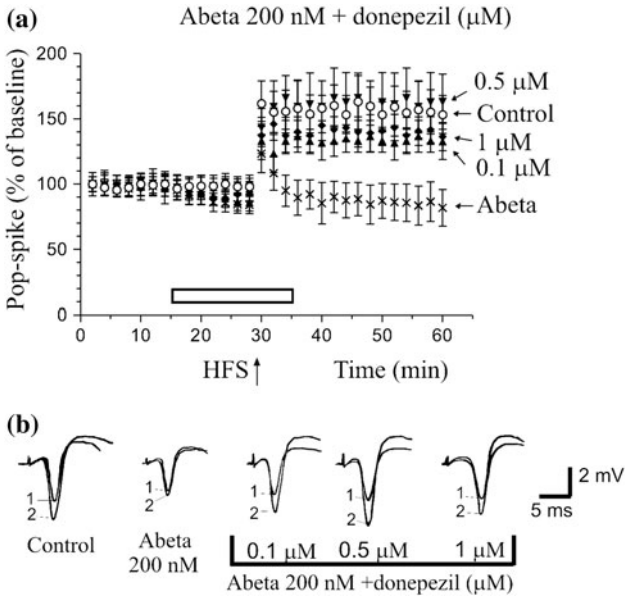

Fig. 2 Effects of donepezil on LTP suppression produced by Abeta in the hippocampal CA1 region. **a** LTP suppression by 200 nM Abeta, and prevention of Abeta effect by low concentrations of donepezil (0.1–1 μM) co-administered with Abeta. Each point is the mean ± SEM of normalized PS amplitude. **b** Example of traces of PS before (*1*) and 30 min after tetanus (*2*) from untreated slices (control) or slices treated with 200 nM Abeta alone or together with a low dose of donepezil (0.1, 0.5 or 1 μM)

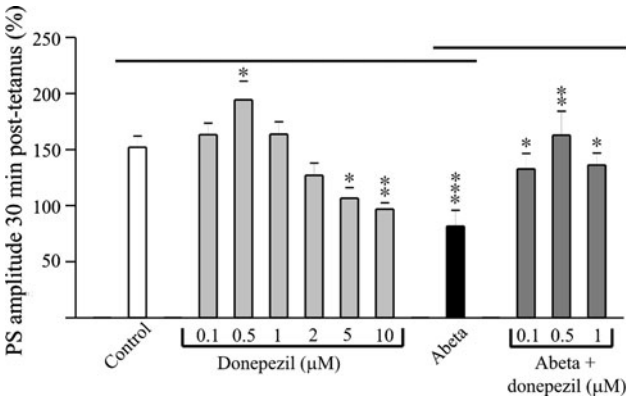

Fig. 3 Average values of PS amplitude 30 min after tetanus in different groups: control, donepezil alone, Abeta alone, or Abeta co-administered with donepezil. Each column is the mean ± SEM, expressed as the percentage of baseline. The effects of Abeta alone and donepezil alone were compared with control group, while the effects of Abeta co-administered with donepezil were compared with Abeta group. *$P < 0.05$, **$P < 0.01$, ***$P < 0.005$

Since NMDRs are the key structures in mechanisms of hippocampal LTP, one could suggest an involvement of NMDRs into the effects of both Abeta and donepezil on LTP in our experiments. Thus, it seemed interesting to study the influence of Abeta and donepezil on NMDA current in hippocampal pyramidal neurons. The experiments were conducted in acute isolated CA1 hippocampal pyramidal neurons using whole-cell patch-clamp technique. Under our experimental conditions (see "Methods" section), the responses evoked by repeated application of 50 μM L-aspartate with 5 μM glycine for 1 s at 60 s intervals gradually decreased during prolonged whole-cell recording ("run-down"). Besides, a progressive increase in NMDA receptor desensitization was also observed. Similar behavior of NMDA current in hippocampal neurons was described by other authors (Rosenmund and Westbrook 1993; Vyklicky 1993). The degree of NMDA current "run-down" varied from cell to cell, and we chose for our experiments only cells with "run-down" no more than 10% after the first ten applications. We recorded NMDA current for 10 min to establish a baseline, and then applied 200 nM Abeta for 15 min followed with 15 min washout. In control group ($n = 10$), the average peak amplitude of NMDA current decreased to 85 ± 7% and 76 ± 9% of the initial amplitude after 25 and 40 min from the first NMDA

response, accordingly. In Abeta group ($n = 10$), the tendency to accelerate the "run-down" of NMDA responses was observed. The peak of NMDA current suppressed to 77 ± 7% after 15 min of Abeta application (25th min of the experiments), and to 66 ± 9% after 15 min of Abeta washout (40th min of the experiments) (Fig. 4). However, these differences were not statistically significant in comparison with corresponding control values. It is also important to note, that Abeta itself did not evoke an inward current in our experiments (data not shown) in contrast to the results by Snyder et al. (2005) obtained in cortical neurons.

Then we studied the influence of donepezil on NMDA responses of hippocampal neurons. Two concentrations of the drug were chosen, 0.5 and 10 μM, which caused maximal increase and suppression of LTP, accordingly, in our experiments. The same protocol of applications, as in the experiments with Abeta, was used. It was found that 0.5 μM donepezil did not affect NMDA responses at all (81 ± 8% after 15 min application, $n = 10$), while 10 μM donepezil caused a rapid and reversible suppression of NMDA responses (65 ± 5% after 15 min application, $n = 10$, $P < 0.05$) (Fig. 5).

Discussion

In the present study, we describe for the first time the effects of wide range of concentrations of donepezil on

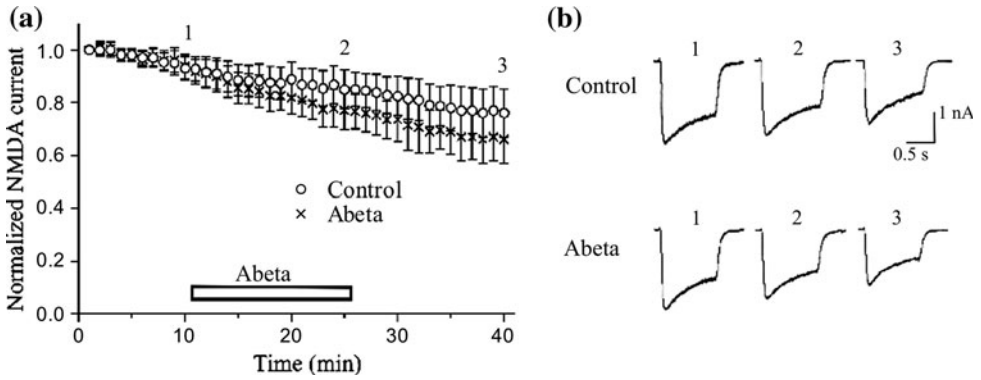

Fig. 4 No effect of Abeta on NMDA current in acutely isolated hippocampal neurons. Currents were evoked at a holding potential of -70 mV in Mg^{2+}-free solution by 1-s applications of 50 μM L-aspartate with 5 μM glycine with interval of 1 min. **a** Time course of changes (mean ± S.E.M) in peak current amplitude recorded from the untreated cells (*open circles*, $n = 10$) and the cells treated for 15 min with 200 nM Abeta (*crosses*, $n = 10$). Currents were normalized to the first application. **b** Currents recorded from an untreated cell (*upper line*) and a cell treated with 200 nM Abeta (*lower line*). The traces were taken at the time points indicated by *numbers*, which correspond to those in the graph shown in (**a**). For a treated cell, these numbers indicate the currents recorded before (*1*), after 15 min Abeta treatment (*2*), and after 15 min washout from Abeta (*3*)

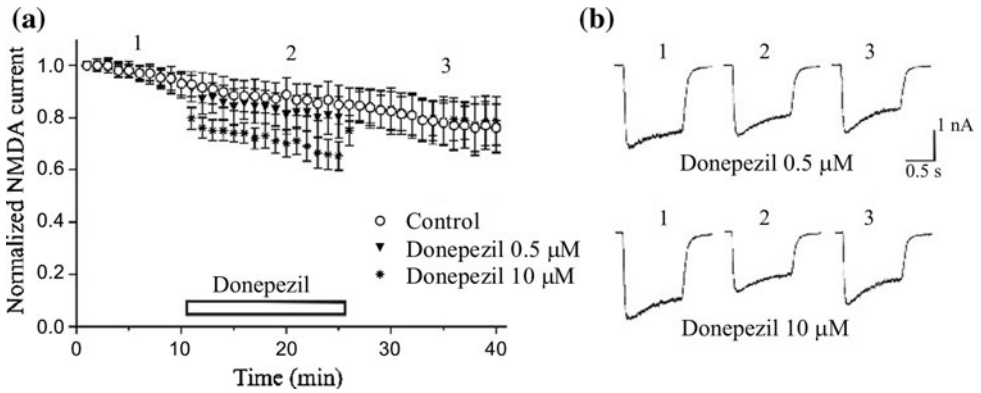

Fig. 5 Donepezil does not change NMDA currents at concentration of 0.5 μM and suppresses the currents at concentration of 10 μM. Currents were evoked at a holding potential of −70 mV in Mg^{2+}-free solution by 1-s applications of 50 μM L-aspartate with 5 μM glycine with interval of 1 min. **a** Time course of changes (mean ± S.E.M) in peak current amplitude recorded from the untreated cells (*open circles*, $n = 10$), the cells treated for 15 min with 0.5 μM donepezil (*filled triangles*, $n = 10$) or 10 μM donepezil (*asterisks*, $n = 10$). Currents were normalized to the first application. **b** Currents recorded from a cell treated with 0.5 μM donepezil (*upper line*) or 10 μM donepezil (*lower line*). The traces were taken at the time points indicated by *numbers*, which correspond to those in the graph shown in (**a**): *1*—before treatment, *2*—after 15 min donepezil treatment, *3*—after 15 min washout from donepezil

control and Abeta-impaired hippocampal LTP. Donepezil was shown to change the amplitude of control LTP with a bell-shaped dose–response curve: 0.5 μM of donepezil significantly increased LTP, while 5 and 10 μM suppressed it. Further, 0.1–1 μM donepezil was shown to rescue hippocampal LTP impaired by Abeta also with a bell-shaped dose–response curve peaked at 0.5 μM. 0.1 μM of donepezil is seemed to be close to therapeutically relevant concentration. Plasma level of the drug in the patients receiving effective doses 10 mg of donepezil hydrochloride per day corresponds approximately 122 nM (Rogers et al. 1998). Additionally, taking into account that, in rodents, the concentration of donepezil in the brain was estimated to be 6–9 times higher than in the plasma (Kosasa et al. 2000), it is conceivable to hypothesize that donepezil concentration in human brain can reach the level of 0.5–1 μM.

A number of studies have demonstrated ability of some other of AChE inhibitors to enhance LTP in brain slices. In rat hippocampal slices, galantamine was shown to augment LTP with a bell-shaped dose–response curve (Moriguchi et al. 2009). The mechanisms of this augmentation were supposed to be associated with α7-type nAChRs and NMDARs activation. In the rat dentate gyrus, physostygmine and tacrine were found to enhance LTP (Welsby et al. 2009), and the effect was interpreted as a result of AChE inhibition. The same mechanism was supposed to be involved into reversal of suppressive action of Abeta on hippocampal LTP by (−)huperzine A (Ye and Qiao 1999).

Induction of LTP at most hippocampal synapses is known to be initiated by Ca^{2+} influx into the postsynaptic dendritic spine via NMDAR channels (Malenka and Bear 2004). One could suggest that NMDRs are involved into mechanisms of the LTP impairment by Abeta as well as into mechanisms of donepezil-induced alteration of control LTP and LTP impaired by Abeta. In the literature, various effects of Abeta on NMDARs functions, both activating (Wu et al. 1995; Molnár et al. 2004; Texidó et al. 2011) and suppressing (Chen et al. 2002; Raymond et al. 2003; Snyder et al. 2005; Lacor et al. 2007; Dewachter et al. 2009) are described. The effects depend on experimental model, as well as Abeta concentration and duration of a treatment. In our experiments, no significant effect of Abeta on NMDA current was observed, and this suggests that the treatment of hippocampal slice with 200 nM Abeta during 15 min before tetanus suppresses LTP in NMDARs-independent manner. This conclusion is consistent with some other authors' opinion concerning mechanisms of Abeta-induced impairment of hippocampal LTP (Ye and Qiao 1999; Raymond et al. 2003; Nomura et al. 2005). One can suppose that Abeta may rather affect a downstream pathway of NMDAR signaling, into which upstream molecules other than NMDRs may converge.

Then, we investigated the influence of donepezil on NMDRs current. Previous investigation of donepezil action on NMDA-induced current was carried out in rat cortical neurons in primary culture (Moriguchi et al. 2005). The authors observed different effects of donepezil in different neurons. In multipolar neurons, NMDA current was decreased by 1–10 μM donepezil, but it was potently augmented by 0.01–100 μM donepezil in bipolar neurons. In our experiments, the effects of two concentrations of donepezil on NMDA currents of rat hippocampal pyramidal neurons were examined, 0.5 and 10 μM, which caused maximal increase and suppression, accordingly, in LTP experiments. No noticeable effect of 0.5 μM donepezil on NMDA currents was observed while 10 μM donepezil significantly suppressed it. The results suggest that the augmentation of control LTP in rat hippocampus by low concentrations of donepezil can hardly be explained by the increase in functional activity of NMDARs. At the same time, suppression of LTP by high concentrations of donepezil can be mediated, at least partially, by the decrease in NMDA currents. But complete inhibition of LTP and only partial depression of NMDA currents by 10 μM donepezil suggest that other mechanisms are also involved. Perhaps, high concentrations of donepezil affect the structures that are insensitive to low therapeutically relevant doses of the drug. For example, potential-dependent ionic channels might contribute to this effect since their blockade with donepezil requires concentration of 5 μM or higher (Solntseva et al. 2007; Yuan et al. 2011).

A likely mechanism for donepezil effects described in this article maybe the modulating action of ACh-system on LTP. This action can be realized in two ways: a rise of ACh level in synaptic cleft due to AChE inhibition (Standridge 2002), and/or facilitation of the functions of nAChRs, especially α4nAChR (Akaike et al. 2010). Widely accepted understanding that ACh is a positive modulator of learning and memory, and the fact that facilitation of LTP can be induced by activation of both muscarinic (Luo et al. 2008) and nicotinic (Kenney and Gould 2008) receptors is in favor of this suggestion.

Finally, the interaction of donepezil with σ1 receptors also might be regarded as possible mechanism for LTP facilitation. The drug was shown to bind to the σ1 receptor with high affinity ($K_i = 14.6$ nM) (Kato et al. 1999), and the involvement of σ1 receptor in the reversal of Abeta-induced amnesic effect by donepezil was described (Meunier et al. 2006).

Acknowledgment This study was supported by Grant 10-04-00169 from the Russian Foundation for Basic Research.

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