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Inactivation of presenilins causes pre-synaptic impairment prior to post-synaptic dysfunction

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Abstract

Synaptic dysfunction is widely thought to be a pathogenic precursor to neurodegeneration in Alzheimer’s disease (AD), and the extent of synaptic loss provides the best correlate for the severity of dementia in AD patients. Presenilins 1 and 2 are the major causative genes of early-onset familial AD. Conditional inactivation of presenilins in the adult cerebral cortex results in synaptic dysfunction and memory impairment, followed by age-dependent neurodegeneration. To characterize further the consequence of presenilin inactivation in the synapse, we evaluated the temporal development of pre-synaptic and post-synaptic deficits in the Schaeffer-collateral pathway of presenilin conditional double knockout (PS cDKO) mice prior to onset of neurodegeneration. Following presenilin inactivation at 4 weeks, synaptic facilitation and probability of neurotransmitter release are impaired in PS cDKO mice at 5 weeks of age, whereas post-synaptic NMDA receptor (NMDAR)-mediated responses are normal at 5 weeks but impaired at 6 weeks of age. Long-term potentiation induced by theta burst stimulation is also reduced in PS cDKO mice at 6 weeks of age. These results show that loss of presenilins results in pre-synaptic deficits in short-term plasticity and probability of neurotransmitter release prior to post-synaptic NMDAR dysfunction, raising the possibility that presenilins may regulate post-synaptic NMDAR function in part via a trans-synaptic mechanism.

Keywords: Alzheimer’s disease, conditional knockout, LTP, neurodegeneration, neurotransmitter release, NMDA receptor, synaptic dysfunction, synaptic facilitation.

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γ-secretase-dependent manner (Yu et al. 2001; Feng et al. 2004; Saura et al. 2004; Tabuchi et al. 2009; Wines-Samuelson et al. 2010).

Synaptic dysfunction is widely thought to be a key pathogenic event before frank neuronal death in AD pathogenesis (Hsia et al. 1999; Saura et al. 2004). Inactivation of presenilin in conditional double knockout (PS cDKO) results in striking pre- and post-synaptic impairments prior to progressive neurodegeneration that resemble key neuropathological features of AD, raising the possibility that partial loss of presenilin function may contribute to synaptic dysfunction and neurodegeneration in AD (Saura et al. 2004; Shen and Kelleher 2007; Zhang et al. 2009; Wines-Samuelson et al. 2010). Further dissection of synaptic dysfunction caused by loss of presenilin may provide additional insight into the mechanisms underlying age-related synaptic loss and neuronal degeneration in AD.

In the current study, we performed a detailed electrophysiological analysis in the hippocampal Schaeffer-collateral pathway to establish temporal development of the pre- and post-synaptic defects caused by loss of presenilin in PS cDKO mice. We found that the pre-synaptic deficits, such as frequency facilitation and Ca²⁺ dependency of facilitation, occur prior to post-synaptic NMDA receptor (NMDAR) deficits. Furthermore, we show that the pre-synaptic deficits are associated with a reduction in release probability. Our study suggests that pre-synaptic deficit in neurotransmitter release is the initial impairment prior to post-synaptic NMDAR-mediated dysfunction in PS cDKO mice.

Materials and methods

Mice

The generation of PS cDKO mice has been previously described (Saura et al. 2004). Briefly, fPS1/fPS1;PS2−/−;CamKII-Cre mice were bred with fPS1/fPS1;PS2−/− mice to obtain PS cDKO mice (fPS1/fPS1;PS2−/−;Cre) and fPS1/fPS1;Cre were bred with fPS1/fPS1 to obtain control mice (fPS1/fPS1). The genetic background of the PS cDKO and control mice was similar in the C57BL/6J29 hybrid background.

Western analysis

Quantitative western blots were carried out as previously described (Ho et al. 2006). Briefly, equal amount of protein were resolved on sodium dodecyl sulfate–polyacrylamide gel electrophoresis and radioisotope [35S]-labeled secondary antibodies were used for quantitative analyses followed by PhosphorImager (Molecular Dynamics, Sunnyvale, CA, USA).

Electrophysiological analysis

Electrophysiology experiments were performed on male PS cDKO mice at various ages. Acute hippocampal slices at 400 μm were prepared using a vibratome 2000 as previously described (Saura et al. 2004). Slices were maintained in a storage chamber containing oxygenized artificial CSF (aCSF in mM: 124 NaCl, 5 KCl, 1.25 NaH₂PO₄, 1.3 MgCl₂, 2.6 CaCl₂, 26 NaHCO₃, 10 glucose, pH 7.4, 310–315 mOsm) at 25°C after 1-h recovery at 30°C. Synaptic responses were evoked at the Schaeffer-collateral pathway by a bipolar concentric metal electrode (500-μs biphasic pulses), and recorded with aCSF-filled glass microelectrodes (1–2 MΩ) extracellularly in CA1 stratum radiatum. The recording chamber and aCSF perfusion solution was kept at 30°C. Long-term potentiation (LTP) was induced by five episodes of theta burst stimulation (TBS) delivered at 0.1 Hz. Each episode contains ten stimulus trains (five pulses at 100 Hz) delivered at 5 Hz. Average responses (mean ± SEM) are expressed as percentage of pre-TBS baseline responses, which were evoked by half-maximum stimulation intensity with 0.2 ms pulses at 0.033 Hz. NMDAR responses were recorded in Mg²⁺-free aCSF containing 10 μM 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) and 100 μM picrotoxin, which block α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor- and GABA type A receptor-mediated responses, respectively. Whole-cell recordings were performed in CA1 pyramidal neurons visually identified with an IR-DIC BX51 Olympus microscope (Olympus Corporation, Tokyo, Japan). Patch pipettes (2–4 MΩ) were filled with internal solution consisting of (in mM): 130 CsCl, 8 KCl, 10 EGTA, 10 HEPES, 5 QX-314, 3 ATP, 0.3 Na₂GTP, pH 7.2, 280–285 mOsm. Chemicals were from Sigma unless otherwise noted. Experimenters were blind to the genotypes of the mice.

Statistics

All data shown are mean ± SEM. Statistical analysis was performed with Student’s t-test, *p < 0.05; **p < 0.01; ***p < 0.001.

Results

Impaired frequency facilitation in PS cDKO mice at 5 weeks of age

Our previous western analysis showed that PS1 expression begins to be reduced in the cerebral cortex of PS cDKO mice between postnatal days 18 and 22 (Yu et al. 2001). At 2 months of age, in addition to spatial and associative memory impairments, marked pre- and post-synaptic defects, including paired-pulse facilitation and NMDAR-mediated responses, are observed in the hippocampal Schaeffer-collateral pathway of PS cDKO mice (Saura et al. 2004). To establish the time course of temporal development of these pre-synaptic and post-synaptic defects, we evaluated pre-synaptic and post-synaptic function in PS cDKO mice before the age of 2 months. Our western analysis showed ~50% reduction of PS1 in the cerebral cortex of PS cDKO mice at 4 weeks of age (Fig. 1a). The residual PS1 in cortical lysates prepared from PS cDKO mice is because of expression of PS1 in glia, interneurons and perhaps a small percentage of excitatory neurons that lack Cre expression (Yu et al. 2001).

To establish the temporal development of pre-synaptic deficits in PS cDKO mice, we analyzed frequency-dependent synaptic facilitation, one form of short-term plasticity that is dependent primarily on pre-synaptic release probability (Pr)
Excitatory post-synaptic currents (EPSCs) were evoked by extracellular stimulation of Schaeffer-collateral commissural fibers. We recorded EPSCs evoked by stimulus trains of 1 and 20 Hz stimulations recorded from control and PS cDKO mice. Values of EPSC amplitude were normalized to the amplitude of first EPSC in stimulation trains. (d) Summary graph comparing frequency dependence of synaptic facilitation in 5-week-old PS cDKO mice. The values in parentheses indicate the number of hippocampal neurons (left) and the number of mice (right) used in each experiment. ***p < 0.001.

Calcium-dependency of synaptic facilitation

To examine whether the deficit in synaptic facilitation in PS cDKO mice at 5 weeks of age is calcium-dependent and can be rescued by higher external Ca\textsuperscript{2+} concentration, we measured calcium-dependence of synaptic facilitation by changing external calcium concentration. Synaptic responses were elicited by stimulus trains containing 300 pulses at 14 Hz. In PS cDKO mice, frequency facilitation deficits were calcium-dependent. Synaptic facilitation was significantly reduced at low external calcium concentration ([Ca\textsuperscript{2+}]\textsubscript{e} = 0.5 mM) in PS cDKO mice (Fig. 2a and c). When [Ca\textsuperscript{2+}]\textsubscript{e} was increased to 2.5 mM, synaptic facilitation was still reduced; however, the difference is much smaller (Fig. 2c). Conversely, synaptic facilitation is indistinguishable at 5 and 7.5 mM external calcium concentration (Fig. 2b and c). We also measured calcium dependency in 4-week-old PS cDKO mice, and found no difference compared with control mice (data not shown), which is consistent with the observation that frequency facilitation underlying physiolog-
ical calcium concentration is normal at 4 weeks of age, but impaired at 5 weeks of age in PS cDKO mice (Fig. 1).

Interestingly, at 2.5 mM external calcium concentration, the decrease of synaptic responses underlying 14 Hz stimulus trains (300 pulses), which is thought to reflect the rate of depletion of releasable vesicles pool, were not affected in PS cDKO mice. Values of EPSP slope were normalized to the first stimulus in a stimulation train. The values in parentheses indicate the number of hippocampal slices (left) and the number of mice (right) used in each experiment.

Fig. 2 Calcium dependency of synaptic facilitation in PS cDKO mice. (a–b) Representative traces of synaptic facilitation from 5-week-old control and PS cDKO mice at external calcium concentration ([Ca²⁺]ₑ = 0.5 and 7.5 mM, respectively). (c) Synaptic responses were elicited by high frequency stimulation at different extracellular calcium concentration ([Ca²⁺]ₑ = 0.5, 2.5, 5.0 and 7.5 mM) between control and PS cDKO mice. Values of EPSP slope were normalized to the first stimulus in a stimulation train. The values in parentheses indicate the number of hippocampal slices (left) and the number of mice (right) used in each experiment.

Fig. 3 Reduced release probability (Pr) in PS cDKO mice. (a) Representative traces of unitary EPSCs recorded in response to short trains from control and PS cDKO mice at 5 weeks of age. Plot of Pr during repetitive stimulation showing reduced Pr at unitary synapses from control and PS cDKO mice. (b) Normal Pr during repetitive stimulation in PS cDKO mice at 4 weeks of age. The values in parentheses indicate the number of hippocampal neurons (left) and the number of mice (right) used in each experiment.

ical calcium concentration is normal at 4 weeks of age, but impaired at 5 weeks of age in PS cDKO mice (Fig. 1). Interestingly, at 2.5 mM external calcium concentration, the decrease of synaptic responses underlying 14 Hz stimulus trains (300 pulses), which is thought to reflect the rate of depletion of releasable vesicles pool, were not affected in
5-week-old PS cDKO mice (averages of last 20 EPSCs in 300-pulse trains were compared; control = 28.8 ± 5.3%; PS cDKO = 31.1 ± 4.4%), arguing against an impairment of synaptic vesicle recycling as a cause of the decreased synaptic facilitation. These results demonstrate that the frequency facilitation deficit caused by presenilin inactivation is calcium-dependent.

Reduced release probability in PS cDKO mice

The calcium-dependence frequency facilitation deficit caused by presenilin inactivation at 5 weeks of age suggests that probability of release (Pr) during repetitive stimulation is reduced in PS cDKO mice. To test this directly, we examined Pr by recording trains of unitary synaptic responses evoked by low intensity stimulation. The plot of occurrence of unitary responses directly reflects the release probability at the single recording synapse. Probability of release during 20 Hz stimulus trains was normal in PS cDKO mice at 4 weeks of age (Fig. 3b), but it was significantly reduced at 5 weeks of age (Fig. 3a). These results show that probability of neurotransmitter release is impaired in PS cDKO mice at 5 weeks of age.

Reduced NMDAR-mediated responses in PS cDKO mice

We next examined the temporal development of postsynaptic deficits in PS cDKO mice by measuring NMDAR-mediated synaptic responses at 5 weeks of age, when pre-synaptic changes in short-term plasticity were observed (Figs 1–3). NMDAR-mediated synaptic responses were measured by pharmacologically applying blockers of AMPA and GABA_A receptors (10 μM CNQX and 100 μM picrotoxin, respectively). We found that input-output curve of NMDAR-mediated synaptic responses, is normal in PS cDKO mice at 5 weeks of age (Fig. 4a). However, at

![Graphs showing NMDAR-mediated responses in PS cDKO mice at 5 and 6 weeks of age.](image)
6 weeks of age, we observed a small but significant reduction in NMDAR-dependent responses in PS cDKO (Fig. 4b). Furthermore, we quantified the ratio of NMDAR- to AMPA receptor-mediated responses recorded from CA1 pyramidal neurons, a more precise measurement in monitoring post-synaptic NMDARs. AMPA receptor-mediated response was recorded at −70 mV holding potential in the presence of Mg²⁺ to block NMDAR-mediated component. NMDAR-mediated response was measured 75 ms after the peak of synaptic responses recorded at +40 mV holding potential. Consistently, we found similar temporal patterns in NMDA/AMPA ratio: normal at 5 weeks and impaired at 6 weeks of age in PS cDKO mice (Fig. 4c).

Next, we measured LTP in hippocampal Schaffer-collateral pathway of PS cDKO mice. LTP was induced by five trains of TBS and the magnitude of LTP measured 60 min after induction was indistinguishable in PS cDKO and control mice at 5 weeks of age (Fig. 4d). However, LTP was significantly impaired in PS cDKO mice at 6 weeks of age (Fig. 4d). Together, these results show that PS cDKO mice exhibit deficits in synaptic transmission (both short and long-term plasticity) and pre-synaptic changes in neurotransmitter release occur prior to the post-synaptic receptor changes in PS cDKO mice.

Discussion

It is well known that the extent of synaptic loss provides the best correlates to the severity of cognitive impairments during the early and late stages of AD (Hanks and Flood 1991; Terry et al. 1991; Braak and Braak 1997). Loss of presenilin function and accumulation of β-amyloid peptides can induce synaptic impairment in the absence of neuronal degeneration (Hsia et al. 1999; Saura et al. 2004; Zhang et al. 2009), suggesting that synaptic dysfunction may be a pathogenic precursor before frank neurodegeneration in AD. Our prior analysis of PS cDKO mice at 2 months of age, before the onset of neurodegeneration, revealed that loss of presenilin function in the adult cerebral cortex causes both pre-synaptic and post-synaptic deficits, such as paired pulse facilitation, NMDAR-mediated responses and LTP (Saura et al. 2004). In the current study, we pursued further the role of presenilins in the synapse by exploring the temporal development of pre-synaptic and post-synaptic deficits in the CA3–CA1 synapse of PS cDKO mice, in which presenilins are inactivated in both CA3 and CA1 hippocampal neurons at 4 weeks of age. We found that impaired synaptic function in PS cDKO mice is age-dependent and the earliest synaptic changes occur at 5 weeks of age, when pre-synaptic deficit in neurotransmitter release is the initial impairment prior to post-synaptic dysfunction. We found that frequency facilitations are selectively impaired in a calcium-dependent manner, whereas use-dependent depression is normal in PS cDKO mice. Furthermore, probability of evoked glutamate release during repetitive stimulus trains is also substantially reduced, providing further evidence for pre-synaptic deficits in short-term plasticity. In contrast, post-synaptic NMDAR-mediated responses are normal at 5 weeks of age in PS cDKO mice. It is not until 6 weeks of age, we observed reduced post-synaptic NMDAR-mediated responses in PS cDKO mice. Our studies suggest that the pre-synaptic deficits occur prior to post-synaptic NMDAR dysfunction in the absence of presenilins at mature synapses, raising the possibility that post-synaptic NMDAR alteration might be caused in part via a trans-synaptic mechanism.

Notably, our data showed that synaptic facilitation is impaired in a calcium-dependent manner in PS cDKO mice, which support the notion that inactivation of presenilins affects calcium homeostasis and induces pre-synaptic deficits. Our recent report using two independent lines of more restricted PS cDKO mice, in which presenilins are inactivated in either CA3 or CA1 neurons, demonstrated that loss of pre-synaptic presenilins alone is sufficient to cause defects in glutamate release and LTP via alterations in intracellular calcium signaling (Zhang et al. 2009). However, inactivation of presenilins in either pre-synaptic CA3 or post-synaptic CA1 neurons alone is insufficient to cause NMDAR deficits, suggesting that both cell-autonomous and trans-synaptic mechanisms are at work in presenilin-dependent NMDAR functions (Fig. 5). The findings from the current study showing NMDAR impairment follows pre-synaptic deficits in PS cDKO mice lacking presenilins in both CA3 and CA1 neurons provide further support for this trans-synaptic mechanism. Thus, LTP deficits in the absence of presenilins are likely caused by both the neurotransmitter release impairment because of loss of pre-synaptic presenilins and the NMDAR dysfunction because of loss of pre-synaptic and post-synaptic presenilins (Fig. 5). These findings raised the possibility that impaired pre-synaptic

Fig. 5 A model depicts how presenilins regulate synaptic function and memory. Presenilins can promote LTP induction and memory via two independent mechanisms: pre-synaptic presenilin regulates probability of glutamate release through its control of calcium release from the ER, whereas both pre-synaptic and post-synaptic presenilins are involved in the regulation of NMDAR functions.
glutamate release and NMDAR function may both play roles in AD pathophysiology.

Impairment in neurotransmitter release may be one of the earliest pathogenic changes prior to neurodegeneration in AD. Recent studies show that PINK1, DJ-1 and Parkin, proteins associated with familial Parkinson’s disease, are crucial for action-potential induced dopamine release from nigrostriatal terminals and striatal synaptic plasticity without detectable neurodegeneration (Goldberg et al. 2005; Kitada et al. 2007, 2009). Together with our observations, it seems possible that reduced neurotransmitter release may represent a convergent mechanism leading to neurodegeneration in affected circuits in AD and Parkinson’s disease, and perhaps other neurodegenerative diseases.

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