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ORIGINAL ARTICLE

Lack of β-amyloid cleaving enzyme-1 (BACE1) impairs long-term synaptic plasticity but enhances granule cell excitability and oscillatory activity in the dentate gyrus in vivo

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Abstract

BACE1 is a β-secretase involved in the cleavage of amyloid precursor protein and the pathogenesis of Alzheimer's disease (AD). The entorhinal cortex and the dentate gyrus are important for learning and memory, which are affected in the early stages of AD. Since BACE1 is a potential target for AD therapy, it is crucial to understand its physiological role in these brain regions. Here, we examined the function of BACE1 in the dentate gyrus. We show that loss of BACE1 in the dentate gyrus leads to increased granule cell excitability, indicated by enhanced efficiency of synaptic potentials to generate granule cell spikes. The increase in granule cell excitability was accompanied by prolonged paired-pulse inhibition, altered network gamma oscillations, and impaired synaptic plasticity at entorhinal-dentate synapses of the perforant path. In summary, this is the first detailed electrophysiological study of BACE1 deletion at the network level in vivo. The results suggest that BACE1 is important for normal dentate gyrus network function. This has implications for the use of BACE1 inhibitors as therapeutics for AD therapy, since BACE1 inhibition could similarly disrupt synaptic plasticity and excitability in the entorhinal–dentate circuitry.

Keywords Electrophysiology · Local field potentials (LFPs) · Population spike · LTP · Alzheimer's disease

Introduction

BACE1 (β-site amyloid precursor protein cleaving enzyme-1) is a β-secretase which cleaves amyloid precursor protein (APP; Vassar et al. 1999; Hussain et al. 1999; Sinha et al. 1999; Yan et al. 1999; Müller et al. 2017), thereby contributing to the generation of β-amyloid (Haass and Selkoe 1993). High BACE1 expression is found in the nervous system with a selective enrichment in the hippocampus (Laird et al. 2005). Although the involvement of BACE1 in the amyloid-induced pathogenesis of AD has been thoroughly studied in vitro and ex vivo (Cai et al. 2001, 2010, 2012; Luo et al. 2001; Fukumoto et al. 2002; Haass 2004), little is known about the physiological role of BACE1 in the brain of live animals. It is important to elucidate BACE1 function in vivo, because BACE1 is a potential therapy target in AD (Yan and Vassar 2014; Oehlrich et al. 2014; Ghosh and Osswald 2014; Vassar 2014; Yan et al. 2016; Ohno 2016; Yan 2017).

The previous work using organotypic hippocampal tissue cultures has shown that BACE1-mediated cleavage of APP,

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which releases β-amyloid, leads to depression of excitatory synaptic transmission (Kamenetz et al. 2003). Experiments in transgenic APP mice indicated that BACE1-mediated cleavage may have also supportive effects on synaptic function (Ma et al. 2007). Later, in vitro studies in BACE1 knockout mice (KOs) demonstrated that BACE1 deletion impairs presynaptic function at synaptic connections between dentate granule cells and CA3 pyramidal neurons (Wang et al. 2008, 2010a, 2014). Similarly, recordings in hippocampal slices of BACE1 KOs revealed alterations in presynaptic short-term plasticity in the CA1 (Laird et al. 2005). Although the early phenotypic characterization of BACE1 KOs reported normal development and normal gross behavior (Luo et al. 2001; Roberds et al. 2001), the BACE1 KO phenotype has been associated with behavioral deficits in learning and memory (Ohno et al. 2004; Laird et al. 2005; Savonenko et al. 2008; Kobayashi et al. 2008) increased mortality, hyperactivity, enhanced locomotion (Dominguez et al. 2005), increased anxiety (Harrison et al. 2003), and epilepsy (Hitt et al. 2010; Hu et al. 2010). In addition, BACE1 has been implicated in the regulation of LTP, spine formation and plasticity (Filser et al. 2015; Zhu et al. 2018b; Blume et al. 2018), hippocampal neurogenesis (Hu et al. 2013), and neuronal excitability by modulating voltage-gated potassium (Sachse et al. 2013; Hessler et al. 2015) or sodium channels (Wong et al. 2005; Dominguez et al. 2005; Kim et al. 2007, 2011; Hu et al. 2010; Huth et al. 2011) (but see also (Hitt et al. 2010); for reviews, see [Yan et al. 2016; Yan 2017; Zhu et al. 2018a)].

Despite these intense investigations of BACE1 (Kandalepas and Vassar 2014; Vassar et al. 2014; Barão et al. 2016; Zhu et al. 2018a), there are still major gaps in our knowledge: the majority of the previous studies have used in vitro preparations of brain tissue, or restricted their investigations to describing the behavioral deficits in BACE1 KOs. Therefore, the function of BACE1 at the synaptic level in vivo remains unclear. Unraveling physiological roles of BACE1 in intact animals is, however, of clinical relevance, because deletion as well as pharmacological blockade of BACE1 could result in significant functional changes. Therefore, we studied in detail the role of BACE1 in the entorhinal-dentate gyrus pathway of live animals by performing local field potential (LFP) recordings (Jedlicka et al. 2011, 2012, 2015, 2018; Vnencak et al. 2015) in anesthetized BACE1-deficient mice. In this way, we tested whether the lack of BACE1 leads to the alterations of neuronal excitability and synaptic plasticity.

Methods

Electrophysiological measurements were performed in adult 14–20-week-old male BACE1 knockout (KO) and control wild-type (WT) mice. All experiments were carried out in accordance with the German laws governing the use of laboratory animals. Every effort was made to minimize animal suffering. The examiner was blind to the genotype. Surgery and electrophysiological procedures were performed as described before (Jedlicka et al. 2011, 2015). First, animals were anesthetized with an intraperitoneal injection of urethane (Sigma-Aldrich, St. Louis, MO, USA; 1.2 g/kg body weight). The depth of anesthesia was estimated by toe pinch reflex and, if needed, additional doses (0.3–1 g/kg) were administered subcutaneously. The body temperature was constantly monitored by a rectal probe and maintained at 37 °C with a thermostatically heating pad. A reference electrode was placed into the subcutaneous tissue suboccipitally. Holes were drilled in the skull, while anesthetized animal was kept in a stereotaxic frame. A bipolar stimulation electrode (NE-200, 0.5 mm tip separation, Rhodes Medical Instruments, USA) was positioned into the angular bundle of the perforant path (3.7 mm posterior to bregma, 2.5 mm lateral to midline, 1.8 mm deep from the brain surface). As a recording electrode, a pulled glass capillary filled with 0.9% NaCl solution was used. Recordings were performed ipsilaterally to stimulation in the granule cell layer of the dentate gyrus (1.7 mm posterior to bregma and 1 mm lateral to midline). The recording electrode was inserted into the brain tissue stepwise in 0.05–0.1 mm increments while monitoring the laminar profile of LFPs (evoked by 500 µA/0.1 ms test stimulus applied at 0.1 Hz) until the response waveform typical for the granule cell layer was observed, usually 1.6-2.0 mm from the brain surface (subdural depth). Stimulation and recordings of evoked potentials were made in the perforant path and in the hilus of the dentate gyrus, respectively. Recordings were performed ipsilaterally to the site of stimulation. Current pulses (30–800 µA with 0.1 or 0.2 s duration) were generated by a stimulus generator STG1004 (Multichannel Systems, Reutlingen, Germany). Recorded LFPs were processed by a preamplifier Grass AC P55 (Grass Technologies, West Warwick, RI, USA) and digitized at 10 kHz by Digidata1440A interface (Molecular Devices, Union City, CA, USA). For offline data processing and analysis, Clampfit 10.2 software (Molecular Devices, Union City, CA, USA) was used. To determine the stimulus–response relationships (input–output curve), the perforant path was stimulated with intensities ranging from 30 to 800 µA/0.1 ms. Three responses per stimulation intensity were recorded and averaged. Next, the amplitudes of the population spike and the slope of the field excitatory postsynaptic potential (fEPSP) were determined. The population spike amplitude was calculated as an average of the amplitude from the first positive peak (a) to the following negative peak (b) and the amplitude from the negative peak to the second positive peak (c), according to the formula: $((a - b) + (c - b))/2$. The slope of fEPSP

was acquired by measuring the steepness of the early positive component of waveform to avoid contamination by the population spike. To quantify the firing ability of the granule cell layer in response to the synaptic drive, a population spike evoked by a given fEPSP slope was determined (E–S-coupling curve). Population spike amplitudes acquired from each input–output measurement were plotted against corresponding fEPSP slopes and the obtained curve was fitted with a Boltzmann function (Jedlicka et al. 2015). Only curves with goodness of fit (*R*-square) greater than 0.8 were further analyzed and the v50 value (i.e., the slope eliciting a spike of half-maximal amplitude for a given input–output measurement) was acquired. To assess presynaptic short-term plasticity, paired-pulse facilitation of the field excitatory potential (PPF) was measured. Two consecutive stimuli were applied at intensities subthreshold for population spike generation with interpulse intervals varying between 15 and 100 ms. Five responses for every interpulse interval were collected and averaged. PPF was determined as relative enhancement of fEPSP amplitude elicited by the paired stimuli. To study paired-pulse inhibition and disinhibition of the population spike (PPI/PPDI), measurements were performed at two different stimulus intensities (800 µA/0.2 ms inducing maximal population spikes and 50–200 µA/0.2 ms inducing population spikes of 1.5–2 mV) at 15–1000 ms interpulse intervals. Five responses at each interpulse interval were recorded and averaged. The population spike inhibition/disinhibition was calculated as a relative change of the population spike amplitude following the first and the second stimulus. PPI/PPDI curves were fitted to the Boltzmann equation and the interpulse interval, at which population spikes of equal amplitude were observed following the first and the second stimuli, was calculated. Long-term potentiation of the synaptic efficacy was induced by theta-burst stimulation (TBS; six series of six trains of six stimuli at 400 Hz with 200 ms between trains and 20 s between series). Before the induction of LTP, baseline responses were recorded for 10 min at 0.1 Hz. The current pulse for baseline stimulation was chosen to evoke the population spike of approximately 1.5 mV. After baseline responses had been recorded, TBS was applied at doubled intensity and duration of stimulus as compared to baseline. Mean baseline slope of fEPSP was calculated from responses prior to the LTP and the potentiation of the fEPSP slope was expressed as a relative increase of fEPSP slope after TBS in comparison to baseline measurements. The latency of the population spike was determined as the time interval from the applied stimulus to the negative peak of the population spike (peak *b*). The shortening of the population spike latency after TBS was expressed as its relative change to the mean population spike latency before LTP induction. Only mice that provided successful LTP induction and stable recordings throughout the experiment were included in the analysis.

For the analysis of spontaneous network activity in the dentate gyrus, spontaneously generated LFPs were recorded for 1 min epochs. Raw data were imported to MATLAB (Mathworks, Natick, MA, USA) and processed by a custom-written script using a freely available chronux plug-in for MATLAB. Raw data were filtered for 0.5–1000 Hz frequencies and subsequently downsampled to 1000 Hz. A multitaper time–frequency spectrogram with a 100 ms moving window and 20 ms overlap was created, and instant gamma power was calculated as the sum of the power density over gamma range frequencies of 25–80 Hz. Gamma bursts were identified as an instant increment in gamma power exceeding the value of a standard deviation (1 STD) calculated over the whole recording period, i.e., 1 min. The frequency and the mean amplitude of gamma bursts were determined and compared between genotypes.

Data were statistically analyzed in the Graph Pad Prism 5.03 software for Windows (GraphPad Software, San Diego, CA, USA). Group data were tested for statistical significance using an unpaired Student's *t* test, and one-way or two-way analysis of variance (ANOVA) with Bonferroni's multiple-comparison posttests as further indicated in the results. A two-tailed *p* value lower than 0.05 was considered significant and marked in figures in the following way: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. Group values were reported as means ± SEM.

Results

Long-term potentiation at excitatory perforant path-granule cell synapses

BACE1 deficit has been reported to impair plasticity at CA3-CA1 synapses in ex vivo hippocampal slices (Filser et al. 2015). To assess the effect of BACE1 deletion on synaptic plasticity at perforant path-granule cell synapses in intact animals, we studied long-term potentiation (LTP) in BACE1 KO mice and their control littermates. First, we induced LTP by theta-burst stimulation of perforant path fibers (see "Methods") and analyzed the LTP-related enhancement of the fEPSP slope. We observed weaker potentiation of the fEPSP slope in BACE1 KO mice comparing to WT controls (Fig. 1a). The relative increase of the fEPSP slope immediately after LTP induction was significantly impaired in BACE1 KO mice (1–10 min, 119 ± 5.7%) as compared to the WT measurements (137.1 ± 3.3%; *t* test, $p < 0.01$) and this difference remained significant throughout the entire recording period (51–60 min, 106.9 ± 6.4% vs. 121.9 ± 3.5%; *t* test, $p < 0.05$). Next, we analyzed the increase in the population spike amplitude after LTP induction and compared the

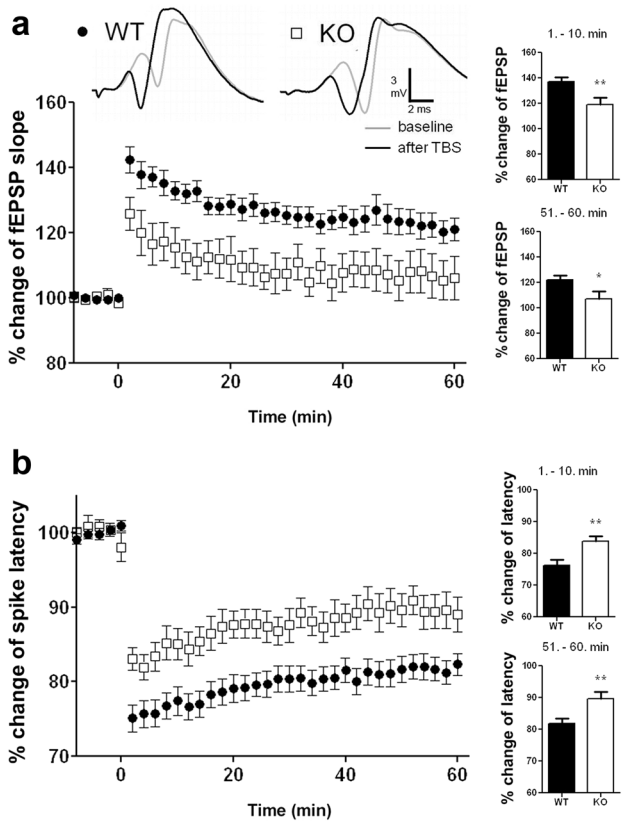

Fig. 1 Decreased LTP at perforant path-granule cell synapses in BACE1 KO mice. **a** Analysis of LTP induced by theta-burst stimulation protocol (six series of six trains of six stimuli at 400 Hz, 200 ms between trains and 20 s between series) showed a significant impairment in LTP induction in BACE1 KO mice ($n=11$) as compared to WT controls ($n=19$). Mean normalized fEPSP slopes over 2 min periods were plotted as a function of time. As displayed in the bar diagrams, mean potentiation of fEPSP slope over 10 min periods 1–10 min and 51–60 min after LTP induction was significantly decreased in BACE1 KO measurements (t test, $p<0.01$, $p<0.05$, respectively). Inset on top, representative recordings from both genotypes before and after LTP induction in gray and black, respectively. **b** After TBS, the latency of the population spike onset gets shorter. Mean normalized LTP-induced shortening of the population spike latency is displayed as a function of time. Shortening of the latency immediately after the TBS as well as at the end of the LTP recording period was significantly attenuated in the BACE1 KO group compared to the WT group. The quantification of the spike latency at 1–10 min and 51–60 min is shown in the bar diagrams (t test, $p<0.01$, $p<0.01$, respectively)

relative growth of population spikes in BACE1 KO measurements (1–10 min, 149.4 ± 13%; 51–60 min, 144.1 ± 9.6%) to WTs (1–10 min, 175.3 ± 11.9%; 51–60 min, 149.2 ± 11.8%). Unlike the fEPSP slope, relative changes in population spike amplitudes did not differ between the two groups (t test, $p>0.05$). Along with the growth of the population spike amplitude, a shortening of spike latency is typically observed after high-frequency stimulation in LTP experiments. Therefore, we quantified changes in the spike latency (Fig. 1b) and detected significantly reduced spike latency shortening in BACE1 KOs after LTP induction (1–10 min, 83.7 ± 1.8%) comparing to WTs (76.2 ± 1.8%; t test, $p<0.01$). This effect lasted until the end of the recording period (51–60 min, 89–65 ± 2.1% vs. 81.9 ± 1.6%; t test, $p<0.01$). Our results demonstrate that BACE1-deficiency impairs long-term synaptic plasticity at perforant path-granule cell synapses.

Basal excitatory synaptic transmission at perforant path-granule cell synapses

BACE1 deletion decreased long-term plasticity of excitatory synapses in the dentate gyrus, but this effect might have been an indirect result of alterations in basal synaptic responses. Therefore, to assess the impact of BACE1 deletion on basal excitatory synaptic transmission, we recorded evoked field excitatory postsynaptic potentials (fEPSPs) in the dentate gyrus of mice lacking BACE1. We analyzed stimulus–response curves for the slope of fEPSPs. The fEPSP slope is known to reflect the number and the strength of excitatory synapses and serves as a measure for synaptic efficacy (Bronzino et al. 1994). For stimulation intensities ranging from 30 to 800 µA, we found that the mean slopes of fEPSP in BACE1 KO mice were weaker than in WT mice, however, this difference was not statistically significant (Fig. 2a, two-way ANOVA, Bonferroni's posttests). Therefore, BACE1 deletion does not result in significantly altered synaptic responses at perforant path-granule cell synapses.

Since BACE1 is targeted to presynaptic terminals (Kandalepas et al. 2013), we evaluated also presynaptic function in BACE1 KOs. For this purpose, we performed paired-pulse facilitation (PPF) measurements at intensities sufficient for perforant path-granule cell synapses activation, but subthreshold for population spike generation. Paired-pulse facilitation (PPF) of fEPSP depends mostly on presynaptic transmitter release mechanisms (Zucker and Regehr 2002) and reflects presynaptically mediated short-term plasticity. We quantified the paired-pulse fEPSP facilitation as the percent ratio of two consecutively evoked fEPSP amplitudes at 15–100 ms interpulse intervals. Our measurements did not show any significant differences in the PPF between BACE1 KO and WT mice (Fig. 2b, two-way ANOVA, Bonferroni's posttests). This finding reveals that BACE1 deletion does not influence presynaptic glutamate release mechanisms at perforant path-granule cell connections.

Population spike generation and excitability of dentate gyrus granule cells

Impaired LTP could be a consequence of reduced excitability of dentate granule cells. Therefore, we studied whether the lack of BACE1 activity impacts the firing ability and excitability of granule cells. To this aim, we analyzed

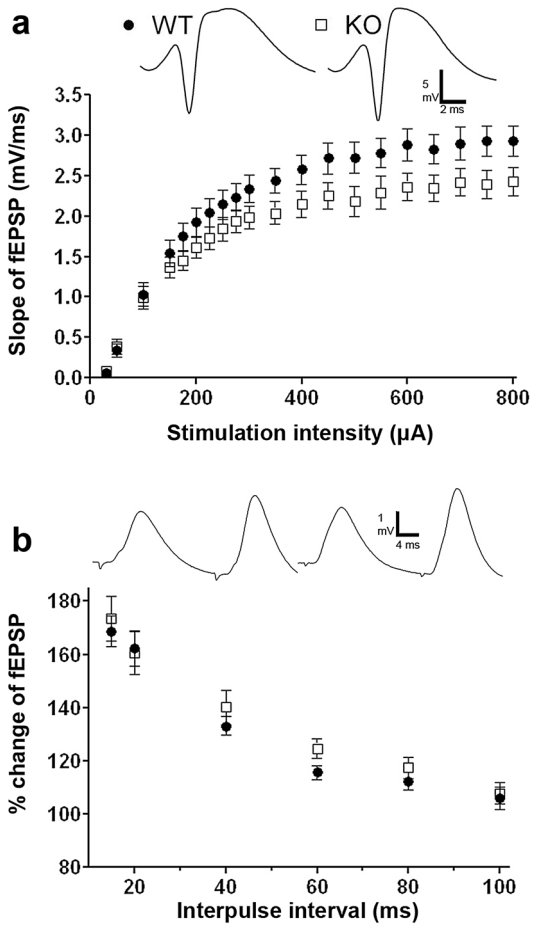

Fig. 2 No significant changes of excitatory synaptic transmission at perforant path-granule cell synapses in BACE1 KO mice. **a** Input–output curve for the slope of the field excitatory postsynaptic potential (fEPSP). The fEPSP slope increases with rising intensity of excitatory synaptic transmission. Although there was a slight trend towards reduced fEPSP slopes in BACE1 KO mice ($n=16$), no significant differences were observed as compared to WT littermates ($n=19$; two-way ANOVA, Bonferroni's posttests, $p>0.05$). Sample responses at 450 µA stimulation intensity are shown on top. **b** Analysis of paired-pulse facilitation (PPF) of the fEPSP did not show any significant difference between BACE1 KO mice ($n=13$) and WT controls ($n=14$; two-way ANOVA, Bonferroni's posttests, $p>0.05$). Unchanged PPF indicates normal transmitter release machinery and presynaptic short-term plasticity in BACE1 KO mice. Representative traces from WT and BACE1 KO measurements at 20 ms interpulse interval are shown in the inset

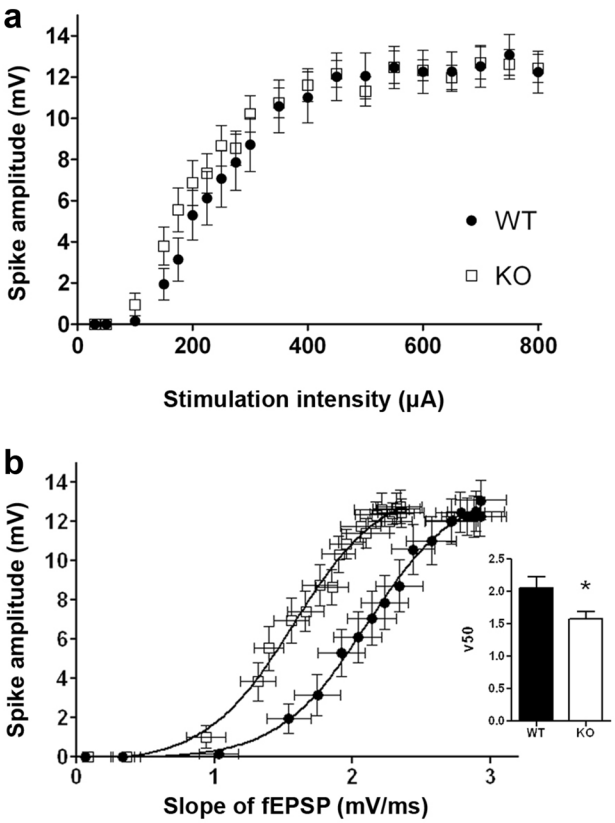

Fig. 3 Increased fEPSP-population spike (E–S) coupling in BACE1 KO mice. **a** Input–output curve for population spike amplitudes acquired from recordings in BACE1 KO animals ($n=16$) and WT controls ($n=19$). The population spike amplitude is a measure for the number and synchrony of firing granule cells. No significant differences were detected between the two groups (two-way ANOVA, Bonferroni's posttests, $p>0.05$). **b** Slopes of fEPSPs from input–output measurements were plotted against corresponding population spike amplitudes. Resulting E–S curves were fitted to the Boltzmann equation and the slope (v50 value) that elicits 50% of maximal spike amplitude was calculated. v50 values acquired from BACE1 KOs ($n=15$) were significantly lower when compared to WTs ($n=19$) revealing enhanced granule cell excitability (t test, $p<0.05$)

population spike amplitudes in input–output recordings. The population spike amplitude grows with increasing synchrony and number of action potentials generated by granule cells (Chauvet and Berger 2002). We recorded granule cell population spikes evoked by perforant path stimulation. Population spike amplitudes acquired from BACE1 KO and WT measurements were compared (Fig. 3a). We observed that population spikes in BACE1 KOs did not differ significantly from WT population spikes, revealing preserved granule cell firing ability in BACE1 KO animals for a given stimulation strength. However, since we noticed a trend toward larger spikes (Fig. 3a) and decreased slopes (Fig. 2a) in KOs relative to WTs, we compared slope values in association with elicited spike amplitudes. This allowed us to analyze the effects of BACE1 deletion on the relationship between synaptic excitatory input (fEPSP slope) to dentate granule cells and their firing output (spike). To this end, we studied fEPSP-spike (E–S) coupling in WTs and BACE1 KOs (Bowden et al. 2012; Jedlicka et al. 2015). For each input–output measurement, the slope of fEPSP was plotted against the corresponding population spike amplitude generating an fEPSP-spike (E–S) curve that was fitted to Boltzmann's function. A slope for eliciting population spike amplitude equal to 50% of the maximal amplitude (value

v50, see "Methods") was calculated for each animal and pooled (Fig. 3b). This analysis revealed a leftward shift in the mean E–S curve for BACE1 KO measurements accompanied by a significantly lower v50 value (1.57 ± 0.12 mV/ms) when compared to WT littermates (2.06 ± 0.18 mV/ms; *t* test, $p < 0.05$). Our results point to an enhanced efficiency of fEPSPs to generate spikes in dentate granule cells of BACE1 KO animals. Thus, instead of reducing granule cell excitability, BACE1 deletion enhances it.

Spontaneous network activity in dentate gyrus

Enhanced excitability, which was detected in the E–S analysis of evoked granule cell responses, could also alter spontaneous granule cell activity. Therefore, we examined spontaneous network activity in the dentate gyrus of BACE1 KO mice. Occurrence of periods with higher activity in gamma frequencies (gamma bursts) is characteristic for spontaneous activity of dentate granule cells (Lacefield et al. 2012). This activity is coupled to oscillations in entorhinal cortex and depends on perforant path input (Csicsvari et al. 2003; Isomura et al. 2006). Analysis of spontaneous LFPs provides valuable information about dentate gyrus network excitability. We recorded spontaneous LFPs in the dentate gyrus for 1 min. Gamma frequency components were extracted from the time–frequency spectrogram and bursts of gamma activity were identified as the instantaneous gamma power exceeding one standard deviation of mean gamma power over the whole recording (Fig. 4). For each measurement, the frequency and the mean peak of gamma bursts power were determined and compared between genotypes. We found that mean values of gamma power in BACE1 KO measurements were significantly higher ($2.8 \pm 0.26 \times 10^{-3}$ mV^2/Hz) when compared to WTs ($0.97 \pm 0.17 \times 10^{-3}$ mV^2/Hz; *t* test, $p < 0.001$). The burst duration was shorter in KOs as compared to WTs (0.17 ± 0.01 s vs. 0.2 ± 0.02 s; *t* test, $p < 0.05$). However, neither the dominant frequency within the bursts nor the frequency, at which gamma bursts occurred, differed between genotypes (1.12 ± 0.13 Hz vs. 1.3 ± 0.3 Hz; *t* test, $p > 0.05$). Setting the threshold for gamma burst recognition to 0.5, 0.75, 1.25 or 1.5 STD, led to the same results, i.e., significantly greater power in gamma bursts in BACE1 KOs, but unchanged frequency of gamma burst occurrence. In summary, in line with enhanced granule cell excitability, our data show increased power of spontaneous gamma activity in the dentate gyrus of BACE1-deficient mice.

Network inhibition in BACE1 KO dentate gyrus

Increased excitability and enhanced power of spontaneous gamma activity in BACE1 KOs are consistent with their epilepsy phenotype, which includes both spontaneous seizures as well as increased susceptibility to pharmacologically

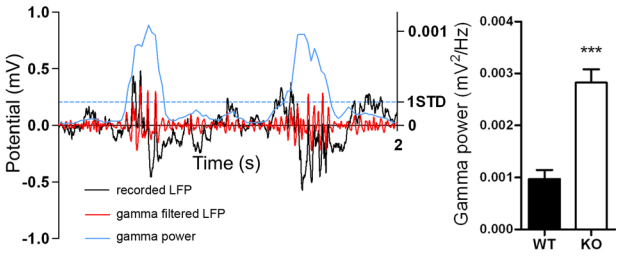

Fig. 4 Increased power of gamma bursts in the dentate gyrus of BACE1 KO mice. Spontaneously generated local field potentials (LFPs) were recorded in the granule cell layer for 1 min. Left diagram represents a sample recording with a duration of 2 s (black line). Red line: the same sample trace filtered for gamma frequencies of 25–80 Hz. Gamma power was extracted from a power spectrogram and gamma bursts were detected as instant gamma power exceeding the threshold set to 1 standard deviation of the mean (blue line). Bar diagram shows comparison of mean peaks of gamma power in gamma bursts between BACE1 KO ($n = 14$) measurements and their WT controls ($n = 9$). In the KO group, the power of gamma activity was significantly higher indicating increased spontaneous activity in the dentate gyrus (*t* test, $p < 0.001$)

induced seizures (Hitt et al. 2010; Hu et al. 2010). Moreover, epilepsy is known to induce compensatory prolongation of paired-pulse network inhibition in the dentate gyrus (O'Sullivan et al. 2016). Therefore, to probe network inhibition in the dentate gyrus of BACE1 KO mice, we performed paired-pulse stimulation measurements and studied changes in evoked population spike amplitudes. The modulation of population spike amplitudes by paired-pulse stimulation depends mainly on the activation of GABAergic network inhibition but also on other network mechanisms (Sloviter 1991; Bronzino et al. 1997; Jedlicka et al. 2010). At short interpulse intervals (< 50 ms), paired-pulse stimulation typically results in the suppression of the population spike amplitude due to the recruitment of network inhibition. In contrast, at longer interpulse intervals (> 50 ms), the inhibition of the spike amplitude turns into a disinhibition. At first, we analyzed relative inhibition and disinhibition of population spike amplitudes following paired-pulse stimulation (PPI/PPDI) at supramaximal stimulation intensities (i.e., stronger intensity than the one needed for maximal spike amplitudes, 800 µA/0.2 ms; see "Methods") to recruit as much network inhibition as possible (Fig. 5a). The PPI/PPDI curve from BACE1 KO animals was significantly right-shifted towards enhanced inhibition as compared to WT measurements. To quantify this shift, PPI/PPDI curves from each recording were fitted to Boltzmann's function and the interpulse interval at which inhibition changes to disinhibition was determined. The comparison between BACE1 KO (52.8 ± 2 ms) and control group (43.5 ± 1.3 ms; *t* test, $p < 0.001$) showed a significantly prolonged interpulse interval, at which PPI turns into PPDI. Subsequently, to rule out that this effect was present only at high stimulation intensities, PPI/PPDI

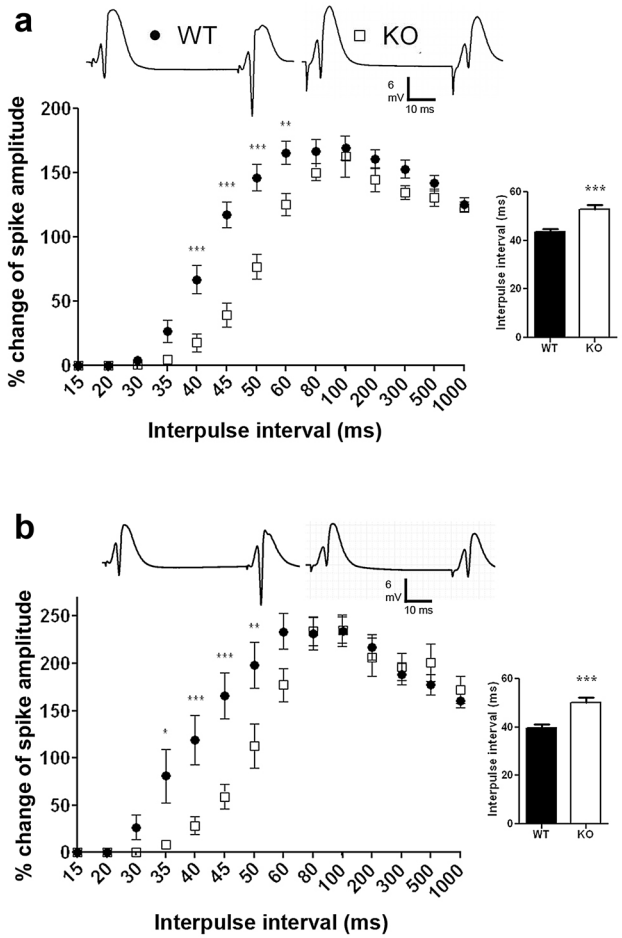

Fig. 5 Prolonged paired-pulse network inhibition in BACE1 KO mice. **a** Paired-pulse inhibition and disinhibition of the population spike amplitude (PPI/PPDI) was examined at 800 µA stimulus intensity. Relative change of the population spike amplitude was plotted against corresponding interpulse interval (IPI). There was a significant rightward shift of the PPI/PPDI curve in BACE1 KO mice ($n=16$) when compared to the WT curve ($n=19$; two-way ANOVA, Bonferroni's posttests as marked in figure). PPI/PPDI curves were fitted to the Boltzmann function and a hypothetical IPI, at which equal amplitude of the first and the second population spike would be detected, was determined and compared between the groups. This IPI was significantly prolonged in BACE1 KO group, as shown in the bar graph (*t* test, $p<0.001$). Right-shifted PPI/PPDI curve and the prolonged IPI for PPI/PPDI turning point in BACE1 KO mice point to prolonged network inhibition. Sample recordings of paired-pulse responses at 50 ms IPI are shown in the inset. **b** PPI/PPDI of the population spike was examined in BACE1 KO mice ($n=13$) and their WT littermates ($n=15$) also at a lower stimulation intensity which evoked a population spike of 1.5–2 mV amplitude. Similarly, a significant rightward shift of the PPI/PPDI curve and a significantly longer mean IPI, at which equal amplitude of the first and the paired population spike would be observed (i.e., PPI/PPDI turning point), were detected in BACE1 KOs (*t* test, $p<0.001$). Sample traces show paired-pulse responses at 50 ms IPI

recordings were repeated at lower stimulation intensities, which were sufficient to reliably evoke population spikes of 1.5–2 mV amplitude (see "Methods"). In line with the observations at strong stimulation intensities (800 µA/0.2 ms), the PPI/PPDI curve from BACE1 KO measurements was shifted to the right also at minimal stimulation intensities. Accordingly, the calculated interpulse interval for turning of PPI to PPDI was significantly longer in BACE1 KO animals (50.3 ± 2 ms) comparing to WT controls (39.6 ± 1.7 ms; *t* test, $p<0.001$). These results indicate that deletion of BACE1 in mice leads to prolonged network inhibition in the dentate gyrus.

Discussion

The main findings of our electrophysiological study can be summarized as follows: BACE1 deletion in the dentate gyrus leads to (1) impaired long-term synaptic plasticity of perforant path synapses, (2) increased coupling of synaptic potentials to the generation of granule cell spikes, (3) increased power of network gamma oscillations, and (4) enhanced paired-pulse inhibition. These results indicate that BACE1 is involved in the regulation of synaptic plasticity and network excitability in the entorhinal-dentate circuitry. This might limit the use of BACE1 inhibition in AD therapy.

In this work, we focused on changes in dentate gyrus network function caused by BACE1-deficiency in vivo. Recent studies in BACE1 KO animals reported increased neuronal excitability and susceptibility to seizures (Hitt et al. 2010; Hu et al. 2010; Hessler et al. 2015), altered presynaptic function (Wang et al. 2008, 2014), and disrupted synaptic plasticity (Laird et al. 2005; Wang et al. 2008; Filser et al. 2015). Therefore, we wondered whether the lack of BACE1 activity leads to similar effects in dentate granule cells and their circuitry in vivo.

We demonstrated that the loss of BACE1 impairs long-term synaptic plasticity at perforant path-granule cell synapses in live animals. This finding is in line with the previously reported defects of LTP in hippocampal areas CA3 and CA1 of BACE1 KOs or upon BACE1 inhibition detected in in vitro preparations (Laird et al. 2005; Wang et al. 2008; Filser et al. 2015; Willem et al. 2015). These studies together with our work reveal impaired LTP at 3 major hippocampal synapses offering a plausible explanation for the observed behavioral abnormities in BACE1 KO mice. The KOs exhibit learning deficits in the Y-maze and the Morris water maze (Ohno et al. 2004; Laird et al. 2005) accompanied by decreased exploratory behavior and anxiety (Harrison et al. 2003). The molecular mechanism of BACE1 involvement in LTP regulation is not fully understood. LTP is known to be dependent on NMDA-receptor activation and Ca^{2+} influx (Nicoll and Roche 2013). However, NMDA

-receptor mediated responses in BACE1 KO hippocampal CA1 region were not changed (Laird et al. 2005). There is a line of evidence that BACE1 interferes with Ca^{2+} metabolism, as LTP deficit in the CA3 region can be rescued by boosting Ca^{2+} concentration or activation of Ca^{2+} channels (Wang et al. 2008, 2010b). Impaired Ca^{2+} signaling and deficient activity-dependent increase in intracellular Ca^{2+} concentration in BACE1 KO likely contributes to impaired synaptic plasticity. Interestingly, recent findings indicate that the lack of BACE1 cleavage activity increases N-terminally extended β-amyloid containing peptides (NTE-peptides), which affect long-term synaptic plasticity in area CA1 (Welzel et al. 2014); see also (Willem et al. 2015). Therefore, it is likely that impaired LTP in BACE1 KOs is a result of several converging pathomechanisms. In addition to APP, many other substrates have been found to undergo cleavage by BACE1 (Hemming et al. 2009; Kuhn et al. 2012; Dislich et al. 2015; Müller et al. 2017) and lately also non-catalytic function of BACE1 has been proposed (Hessler et al. 2015; Lehnert et al. 2016) suggesting multiple regulatory functions of BACE1 under physiological and pathological conditions (Yan 2017).

To determine whether the LTP deficit is associated with changes in basal excitatory transmission at perforant path-granule cell synapses, we analyzed input–output responses for the fEPSP slope in BACE1 KO mice. We found that there was a trend toward decreased fEPSP slopes but no significant difference when statistically comparing KOs to WT controls, indicating the lack of dramatic changes in glutamatergic transmission. This observation is in line with a previous study in acute slices, where BACE1 deficiency did not significantly alter fEPSP slopes at Schaffer collateral CA3-CA1 synapses (Laird et al. 2005). Similarly, the recent patch-clamp studies showed alterations in mEPSC frequency but unchanged mEPSC amplitudes in the CA3 region (Wang et al. 2014) and also at excitatory synapses in neocortex (Filser et al. 2015) in BACE1-defficient mice. Moreover, the latter study reported normal spine density in the somatosensory cortex of BACE1 KO mice. On the other hand, pharmacological blockage of BACE1 revealed a regulatory role of BACE1 in synaptic transmission and structural plasticity of spines. Prolonged pharmacological inhibition of BACE1 disrupted spine dynamics in neocortical pyramidal cells and attenuated the fEPSP slopes in CA1 [(Filser et al. 2015); see also (Zhu et al. 2018b)]. This seeming discrepancy with fEPSP slope recordings in the dentate gyrus is likely to be explained by the developmental homeostatic mechanisms compensating for the early whole-body genetic loss of BACE1 activity as compared to the lack of compensation after pharmacological BACE1 inhibition. Alternatively, different results may reflect different BACE1-dependent signaling mechanisms at entorhinal–dentate synapses and CA3–CA1 synapses. Such region-specific differences in signaling have been previously described for long-term synaptic plasticity (Cooke et al. 2006). Taken together, the conventional BACE1 deletion does not strongly impair excitatory synaptic transmission at perforant path-granule cell synapses in vivo. Conditional cell-type specific knockout of BACE1 or virus-mediated region-specific knockdown of BACE1 is needed to determine the effects of an acute complete loss of BACE1.

Since BACE1 is present at presynaptic terminals (Laird et al. 2005), we hypothesized that it could be involved in the regulation of presynaptic function. Previously, enhanced paired-pulse facilitation following double-pulse stimulation in BACE1 KOs was observed in hippocampal acute slices at perforant path-CA1 synapses (Laird et al. 2005) and at mossy fiber-CA3 synapses (Wang et al. 2008, 2014). In contrast to these earlier studies, our in vivo data did not show any changes of presynaptically mediated paired-pulse facilitation of fEPSPs at perforant path-granule cell synaptic terminals. Thus, whereas BACE1 seems to play a significant role in presynaptic function at the other excitatory synapses in the hippocampus, it is likely that the effect of BACE1 deletion is not detectable at perforant path-granule cell synapses in the anatomically intact dentate gyrus network. As in the case of above-mentioned postsynaptic responses, this might again reflect region-specific differences between synapses in the dentate gyrus and the CA3/CA1.

When analyzing the fEPSP slope-population spike coupling, we detected strongly increased excitability of BACE1 KO granule cells. In addition, recordings of spontaneous activity in the BACE1-deficient dentate gyrus revealed increased power in gamma oscillations, which is also in line with the enhanced activity of granule cells. BACE1 has been reported to be involved in the processing of voltage-gated sodium channels (Kim et al. 2007; Huth et al. 2011). Thus, altered excitability might be a result of changed membrane levels of voltage-gated sodium channels [(Hu et al. 2010; Kim et al. 2011); but see also (Hitt et al. 2010)]. A recent study reported that increased excitability in BACE1-deficient CA1 region is, at least in part, caused by diminished M-channel activity [(Hessler et al. 2015); see also (Sachse et al. 2013)].

Upregulated excitability of principal neurons in the hippocampus leads to higher susceptibility to seizures in BACE1 KO animals (Kobayashi et al. 2008; Hitt et al. 2010; Hu et al. 2010; Hessler et al. 2015). Epilepsy triggers compensatory enhancement of PPI in the dentate gyrus (O'Sullivan et al. 2016). Therefore, we evaluated network excitability in the BACE1 KO dentate gyrus by measuring PPI/PPDI of the population spike. Our experiments, both at minimal as well as supramaximal stimulation intensities, showed significantly prolonged network inhibition in BACE1 KO mice. Interestingly, measurements at inhibitory neuron-CA3 synapses in the CA3 region revealed

stronger paired-pulse facilitation of IPSCs in BACE1 KO slices (Wang et al. 2014). In this context, increased paired-pulse facilitation of GABA release at inhibitory synapses could be one possible mechanism of more effective network inhibition in the dentate gyrus. However, mIPSC amplitude was unchanged and mIPSC frequency decreased in the CA3 of BACE1 KOs (Wang et al. 2014), suggesting that the enhancement of hippocampal paired-pulse network inhibition in the dentate gyrus might not be mediated by changes in phasic inhibition but rather by upregulation of tonic GABAergic inhibition. Indeed, it is well known that epilepsy may lead to robust compensatory enhancement of tonic GABAergic inhibition in the dentate gyrus (Yu et al. 2013; Lee and Liou 2013; Li et al. 2013). Similarly, enhanced paired-pulse inhibition of population spikes has been repeatedly observed in animals with epilepsy (de Jonge and Racine 1987; Stringer and Lothman 1989; Wilson et al. 1998) including our previous work (Jedlicka et al. 2009; O'Sullivan et al. 2016). Thus, stronger paired-pulse network inhibition in the BACE1-deficient dentate gyrus is very likely a compensatory mechanism for attenuating pathologically increased granule cell excitability, thereby protecting the dentate gate (Krook-Magnuson et al. 2015) from epilepsy.

Because of its contribution to the formation of amyloid β, BACE1 is considered a potential target for AD therapy. Indeed, it has been suggested that BACE1 inhibition might mitigate Aβ deposition and, thus, emergence of an AD phenotype [(Fukumoto et al. 2002; Giusti-Rodríguez et al. 2011; Mattsson et al. 2012; Peters et al. 2018); reviewed by (Yan and Vassar 2014; Vassar 2014)]. However, while this may be the case, our in vivo analysis of BACE1-deficient mice suggests that removal or complete suppression of BACE1 could lead to deficits in synaptic and neuronal physiology in the dentate gyrus. Since dentate granule cells are needed for pattern separation (Leutgeb et al. 2007), therapeutics strongly suppressing BACE1 could worsen spatial learning of AD patients which would limit their usefulness (Barão et al. 2016). Since earlier in vitro studies performed in the CA1 and CA3 regions of the hippocampus have also reported adverse functional effects of BACE1 inhibition (Zhu et al. 2018a), BACE1 inhibitors may, furthermore, impair other hippocampus-dependent forms of learning. Further studies are needed to test whether partial BACE1 inhibition or BACE1 inhibition in AD mice models leads to similar adverse effects. Nevertheless, our observations reported in this study, earlier in vitro work on other areas of the hippocampus, and the lack of significant therapeutic effects of a BACE1 inhibitor in a clinical study (Egan et al. 2018) suggest that AD therapies targeting BACE1 may need to be carefully calibrated and/or complemented or replaced by the other medications in the therapy of AD.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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