Brief Communications

BACE1 Knock-Outs Display Deficits in Activity-Dependent Potentiation of Synaptic Transmission at Mossy Fiber to CA3 Synapses in the Hippocampus

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β-Amyloid precursor protein cleavage enzyme 1 (BACE1) has been identified as a major neuronal β-secretase critical for the formation of β-amyloid (Aβ) peptide, which is thought responsible for the pathology of Alzheimer's disease (AD). Therefore, BACE1 is one of the key therapeutic targets that can prevent the progression of AD. Previous studies showed that knocking out the BACE1 gene prevents Aβ formation, but results in behavioral deficits and specific synaptic dysfunctions at Schaffer collateral to CA1 synapses. However, BACE1 protein is most highly expressed at the mossy fiber projections in CA3. Here, we report that BACE1 knock-out mice display reduced presynaptic function, as measured by an increase in paired-pulse facilitation ratio. More dramatically, mossy fiber long-term potentiation (LTP), which is normally expressed via an increase in presynaptic release, was eliminated in the knock-outs. Although long-term depression was slightly larger in the BACE1 knock-outs, it could not be reversed. The specific deficit in mossy fiber LTP was upstream of cAMP signaling and could be "rescued" by transiently elevating extracellular Ca^{2+} concentration. These results suggest that BACE1 may play a critical role in regulating presynaptic function, especially activity-dependent strengthening of presynaptic release, at mossy fiber synapses.

Key words: **long-term potentiation; long-term depression; presynaptic; paired-pulse facilitation; beta-secretase; Alzheimer's disease**

Introduction

Alzheimer's disease (AD) is the most prevalent form of senile dementia. Current treatment of AD remains limited, and there is no effective disease-modifying treatment as of yet (Citron, 2004b). It is widely believed that AD is initiated as a synaptic dysfunction which correlates with the loss of memory function in the early stages of the disease (Selkoe, 2002). A current hypothesis states that overproduction of β-amyloid (Aβ) peptide initiates the pathogenesis of AD (Hardy and Selkoe, 2002; Citron, 2004b; Walsh and Selkoe, 2007). Aβ is produced by the sequential cleavage of amyloid precursor proteins (APPs) by β- and γ-secretases which are one of the major disease-modifying targets to treat AD (Citron, 2004b). However, it became apparent that γ-secretase processes other critical substrates essential for normal cell development and function, such as Notch (Sisodia and St George-Hyslop, 2002; Selkoe and Kopan, 2003). Therefore, inhibiting β-secretase is now receiving renewed attention (Vassar, 2002; Citron, 2004a,b). The amount and activity of β-secretase is elevated in sporadic AD brains (Yang et al., 2003; Li et al., 2004; Zhao et al., 2007), further suggesting that effective methods to reduce its activity may be beneficial to a large population of AD patients.

A transmembrane aspartic protease, β-site APP cleavage enzyme 1 (BACE1), was identified as the major neuronal β-secretase (Hussain et al., 1999; Sinha et al., 1999; Vassar et al., 1999; Yan et al., 1999). BACE1 knock-out (KO) mice were generated to determine the functional consequences of chronically inhibiting the activity of β-secretase. Initial characterization of the BACE1 knock-outs suggested that there are no gross anatomical or functional abnormalities (Luo et al., 2001, 2003). Moreover, knocking out BACE1 in APP transgenic lines, which normally develop Aβ plaques and behavioral deficits, essentially alleviated the AD symptoms (Luo et al., 2003; Ohno et al., 2004; Laird et al., 2005). However, recent studies, including our own, showed that BACE1 knock-outs display specific dysfunctions in synaptic transmission and plasticity (Ohno et al., 2004; Laird et al., 2005), as well as behavioral deficits (Harrison et al., 2003; Laird et al., 2005; Savonenko et al., 2008). Although all of the studies characterizing synaptic function of BACE1 knock-outs thus far have been performed in the CA1 region of the hippocampus (Ohno et al., 2004; Laird et al., 2005; Ma et al., 2007), the expression of BACE1 is most prominent in the mossy fiber terminals that synapse onto CA3 pyramidal neurons (Laird et al., 2005; Zhao et al., 2007). Therefore, we examined synaptic function and plasticity of the BACE1 knock-outs at the mossy fiber synapses.

Materials and Methods

Animals. All mice used (BACE1 +/+ and −/−) were derived from heterozygous breeders (+/−) as described previously (Laird et al., 2005). The Institutional Animal Care and Use Committees of both University of

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Maryland, College Park and Johns Hopkins University approved all procedures involving animals.

Electrophysiological recordings. Hippocampal slices (400 μm thick) were prepared from adult (3–6 months old) male BACE1 knock-out and wild-type (WT) mice as described previously (Laird et al., 2005). Briefly, hippocampi were sliced in ice-cold dissection buffer (in mM: 212.7 sucrose, 2.6 KCl, 1.23 NaH_2PO_4, 26 $NaHCO_3$, 10 dextrose, $MgCl_2$, and 1 $CaCl_2$, saturated with 5% CO_2 and 95% O_2). Recordings were done in a submersion-type recording chamber perfused with artificial CSF (ACSF) (in mM: 124 NaCl, 5 KCl, 1.25 NaH_2PO_4, 26 $NaHCO_3$, 10 dextrose, 1.5 $MgCl_2$, and 2.5 $CaCl_2$, saturated with 5% CO_2 and 95% O_2, 29.5–30.5°C, 2 ml/min). Synaptic responses were evoked through bipolar stimulating electrodes (double-barreled borosilicate glass capillaries; Sutter Instrument), placed in the dentate granule cell layer to activate the mossy fibers with pulse durations of 0.2 ms (baseline stimulation, 0.067 Hz), and recorded extracellularly in the stratum lucidum of CA3. Both the stimulating and recording electrodes were filled with ACSF. To induce long-term potentiation (LTP), three trains of 100 Hz (1 s) stimuli were given at 20 s intervals. Long-term depression (LTD) was induced by a paired-pulse 1 Hz protocol [interstimulus interval (ISI), 50 ms; 15 min]. For measurement of paired-pulse facilitation (PPF), ISIs of 25, 50, 100, 200, 400, 1000, and 2000 ms were used. In some experiments, extracellular Ca^{2+} concentration was increased to 5.0 mM for 10 min before delivering high-frequency stimulation (HFS) (Castillo et al., 2002). To activate cAMP production, 50 μM forskolin (Sigma-Aldrich) was applied for 5 min. All experiments were done in the presence of 100 μM DL-APV (DL-2-amino-5-phosphonovaleric acid) (Sigma-Aldrich) to block NMDA receptors. At the end of each experiment, 1 μM (2*S*,2′*R*,3′*R*)-2-(2′,3′-dicarboxycyclopropyl)glycine (DCG-IV) (Tocris Bioscience) was added, and blockade ≥80% were taken to be mossy fiber inputs. Field potential (FP) slopes were measured, and data are expressed as mean ± SE of mean.

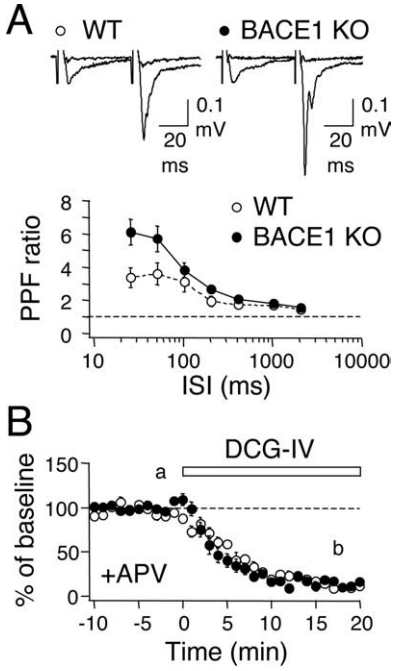

Figure 1. BACE1 knock-outs display a reduction in presynaptic function at the mossy fiber synapses. ***A***, Larger PPF ratio in BACE1 knock-outs. The difference between WT (white circles) and KOs (black circles) are significant at 25 and 50 ms ISIs. Top, Representative FP traces of paired-pulse stimulation at 50 ms ISI before and after DCG-IV application in wild type and knockout. The traces were taken from time points indicated (a and b) in the graph in ***B***. ***B***, Application of group II mGluR agonist (1 μM DCG-IV) reduces mossy fiber synaptic transmission in WT (white circles) and KOs (black circles).

Results

Reduction in presynaptic function at mossy fiber synapses in BACE1 knock-outs

We observed previously that mossy fiber terminals are enriched in BACE1 protein compared with other hippocampal subfields (Laird et al., 2005). Therefore, we hypothesized that BACE1 knock-outs may exhibit alterations in synaptic transmission and plasticity at this particular set of synapses. We first measured presynaptic function by comparing PPF ratio at various ISIs. We found a significant interaction between the genotype and ISIs (two-factor ANOVA, genotype × ISI: $F_{(6, 203)} = 2.586$, $p < 0.02$), particularly BACE1 KOs, displayed larger PPF ratios at shorter ISIs (25 ms ISI: WT, 3.4 ± 0.57; KO, 6.1 ± 0.79; 50 ms ISI: WT, 3.6 ± 0.65, $n = 14$; KO, 5.7 ± 0.77, $n = 17$; Fisher's PLSD *post hoc* test, $p < 0.002$ for 25 and 50 ms ISI between WT and KO) (Fig. 1*A*). The increase in PPF ratio suggests a reduction in presynaptic release. Synaptic transmission at mossy fiber to CA3 synapses display sensitivity to group II metabotropic glutamate receptor (mGluR) agonists (Nicoll and Schmitz, 2005). Bath application of 1 μM DCG-IV at the end of the recording produced a comparable reduction in basal synaptic transmission in both knock-outs and wild types (WT, 12 ± 4% of baseline at 20 min DCG-IV, $n = 14$; KO, 11 ± 2%, $n = 17$) (Fig. 1*B*).

Activity-dependent synaptic strengthening at mossy fiber synapses is abolished in BACE1 knock-outs

Next, we examined whether knocking out BACE1 affects synaptic plasticity at the mossy fiber synapses. We first compared LTP induced by HFS (3 × 100 Hz, 1 s). BACE1 knock-outs showed a larger initial potentiation, suggesting an enhanced facilitation during HFS; however, the responses relaxed back to baseline by 1 h (WT: 149 ± 10% of baseline at 1 h after HFS, $n = 13$ slices from 6 mice; KO: 96 ± 7%, $n = 16$ slices from 7 mice; *t* test, $p < 0.01$) (Fig. 2*A*). Consistent with a presynaptic locus of expression, LTP in wild types was accompanied by a decrease in PPF ratio measured at 50 ms ISI (baseline, 3.1 ± 0.5; 1 h after HFS, 2.6 ± 0.4; $n = 13$ slices from 6 mice; paired *t* test, $p < 0.03$), but knock-outs displayed a trend of a decrease in PPF ratio that returned to basal levels at 1 h (baseline, 5.9 ± 1.0; 20 min after HFS, 3.6 ± 0.5; 1 h after HFS, 6.1 ± 1.2; $n = 16$ slices from 7 mice; ANOVA, $F_{(2,45)} = 2.018$; $p = 0.1$).

To test LTD, we used a paired-pulse 1 Hz protocol [PP-1 Hz (15 min)], because a standard 1 Hz (15 min) protocol (Kobayashi et al., 1996) failed to produce LTD in the wild types at the ages used for our study (data not shown). LTD induced by the PP-1 Hz was slightly, but significantly, larger in BACE1 knock-outs (WT: 75 ± 4.3% of baseline at 1 h after onset of PP-1 Hz, $n = 7$ slices from 5 mice; KO: 62 ± 3.8% of baseline, $n = 6$ slices from 4 mice; *t* test, $p < 0.04$) (Fig. 2*B*). This form of LTD did not significantly change PPF ratio either in wild types or knock-outs (WT: baseline, 3.8 ± 1.0; 1 h after PP 1 Hz, 3.2 ± 0.9, $n = 6$ slices from 4 mice; paired *t* test, $p = 0.16$; KO: baseline, 7.1 ± 1.5; 1 h after PP 1 Hz, 5.5 ± 1.1, $n = 6$ slices from 4 mice; paired *t* test, $p = 0.10$). Unlike in wild types, HFS failed to reverse LTD in the knock-outs (WT: 195 ± 28.0% of renormalized baseline at 1 h after HFS, $n = 6$ slices from 4 mice; KO: 100 ± 5.4%, $n = 6$ slices from 4 mice; *t* test, $p < 0.02$) (Fig. 2*B*).

Rescue of mossy fiber LTP in BACE1 knock-outs by increasing extracellular Ca^{2+} concentration

Mossy fiber LTP is triggered by a rise in presynaptic Ca^{2+} (Castillo et al., 1994) and a further recruitment of cAMP-dependent signaling mechanisms (Nicoll and Schmitz, 2005). Therefore, we investigated whether the lack of mossy fiber LTP in

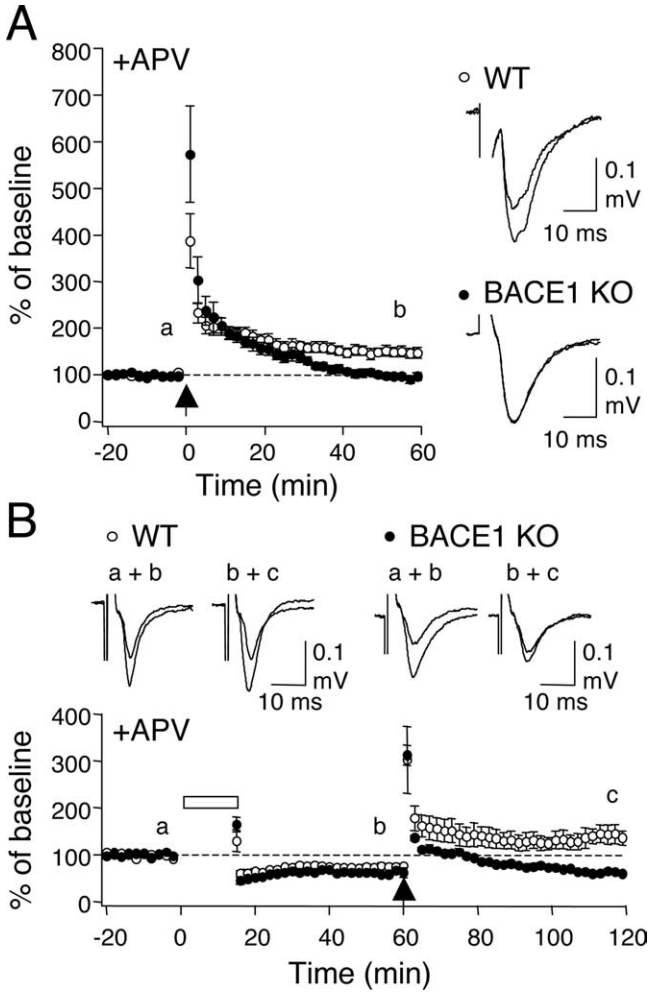

Figure 2. Absence of activity-dependent potentiation at mossy fiber synapses in BACE1 knock-outs. ***A***, Mossy fiber LTP is absent in BACE1 knock-outs. Left, Summary graph plotting changes in normalized field potential against time. The arrow depicts when HFS (100 Hz, 1 s × 3) was delivered. Note that knock-outs (black circles) showed larger posttetanic potentiation but no LTP when compared with wild-types (white circles). Right, Suafterimposed representative FP traces taken from wild type and knock-outs at times indicated in the left panel (a, b). ***B***, BACE1 knock-outs show a slightly larger LTD but no dedepression. Bottom, Summary graph of the averages. The bar and arrow indicate delivery of PP-1 Hz (15 min) and HFS (100 Hz, 1 s × 3), respectively. Top, Representative FP traces taken at times indicated in the summary graph (a–c).

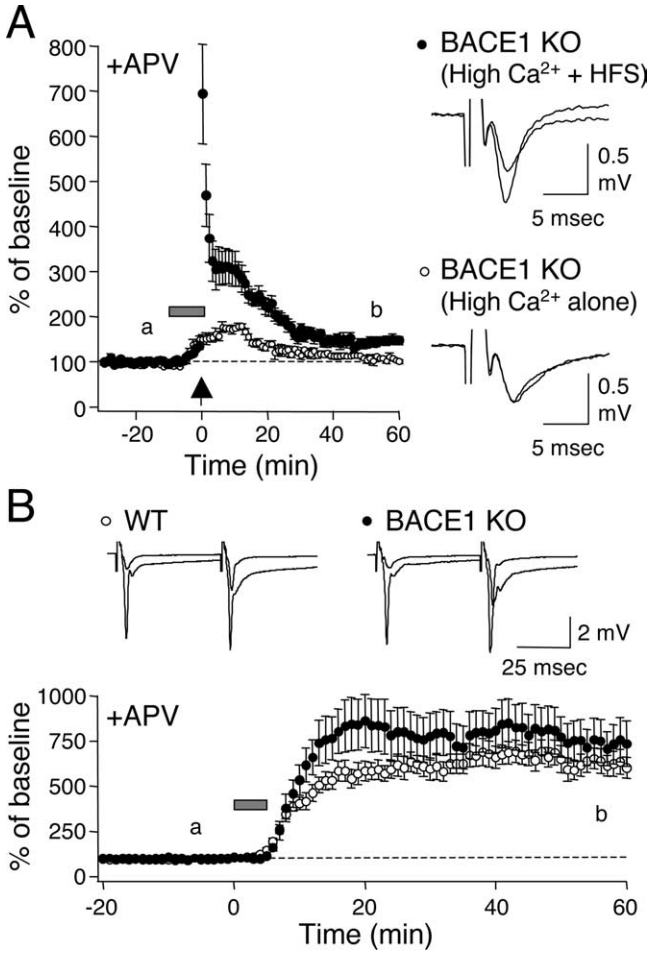

Figure 3. BACE1 knock-outs express mossy fiber LTP under high extracellular Ca^{2+} and produce normal forskolin-induced potentiation. ***A***, Transient elevation of external Ca^{2+} concentration (5 mM Ca^{2+}, 10 min; gray bar) rescued mossy fiber LTP in knock-outs (black circles). Increasing Ca^{2+} alone produced only a transient potentiation (open circles). The arrow depicts when HFS (100 Hz, 1 s × 3) was delivered. Right, Representative traces taken at times indicated (left graph, a and b). ***B***, Transient application of forskolin (50 μM, 5 min; gray bar) potentiated mossy fiber synaptic transmission in wild types (open circles) and knock-outs (black circles) to the same magnitude. Top, Representative traces taken at times indicated (bottom panel, a and b).

BACE1 knock-outs is attributable to abnormal regulation of presynaptic Ca^{2+} or signaling downstream. We found that transiently increasing the concentration of extracellular Ca^{2+} (from 2.5 to 5 mM) during HFS recovered mossy fiber LTP in BACE1 knock-outs (137 ± 7.9% of baseline at 1 h after HFS, $n = 9$ slices from 6 mice; paired t test, $p < 0.01$) (Fig. 3*A*). Furthermore, LTP was accompanied by a decrease in PPF ratio measured at 50 ms ISI (baseline, 4.2 ± 0.7; 1 h after HFS, 2.4 ± 0.4; $n = 9$ slices from 6 mice; paired t test, $p < 0.01$) consistent with a presynaptic expression. Increasing external Ca^{2+} concentration alone produced only a transient potentiation (110 ± 4.8% of baseline at 1 h after Ca^{2+}; $n = 4$ slices from 2 mice; paired t test, $p = 0.13$) (Fig. 3*A*).

To further confirm whether signaling downstream of the Ca^{2+} signal is intact in BACE1 knock-outs, we directly activated cAMP signaling by a brief application of an adenylyl cyclase activator forskolin. This caused a dramatic enhancement of synaptic transmission in both wild types and knock-outs to similar magnitudes (WT: 622.5 ± 57.8% of baseline at 1 h after forskolin, $n =$ 7 slices from 5 mice; KO: 741.8 ± 110.1%, $n = 7$ slices from 4 mice; t test, $p = 0.36$) (Fig. 3*B*). This was accompanied by a significant decrease in PPF ratio in both genotypes (WT: baseline, 3.2 ± 0.34; 1 h after forskolin, 1.5 ± 0.15, $n = 7$ slices from 5 mice; paired t test, $p < 0.01$; KO: baseline, 4.9 ± 0.63; 1 h after forskolin, 1.7 ± 0.16, $n = 7$ slices from 4 mice; paired t test, $p < 0.01$), consistent with a presynaptic mechanism of potentiation. This demonstrates that the presynaptic deficits seen in BACE1 knock-outs are upstream of cAMP signaling.

Discussion

We found that BACE1 knock-outs display severe deficits in presynaptic function at mossy fiber synapses in CA3: a reduction in presynaptic release and an absence of mossy fiber LTP. In addition, BACE1 knock-outs exhibited a slightly larger LTD which could not be reversed. These results suggest that BACE1 function is critical for normal synaptic transmission and plasticity, especially activity-dependent potentiation, at these synapses. We further found that the specific deficit in mossy fiber LTP in BACE1 knock-outs can be rescued by increasing extracellular Ca^{2+} con-

centration. Because a direct activation of cAMP production was not impaired in the BACE1 knock-outs, our data suggest that the presynaptic dysfunction is likely at the level of presynaptic Ca^{2+} regulation.

Previous studies suggest that BACE1 is highly localized to presynaptic terminals, especially at the mossy fiber boutons in the CA3 (Laird et al., 2005; Zhao et al., 2007). This localization is consistent with our observation of a deficit in presynaptic function and plasticity at this synapse. Together with our previous results from the CA1 also showing an increase in PPF ratio (Laird et al., 2005), these results indicate that BACE1 may play a general role in regulating presynaptic function under physiological conditions. However, whether presynaptic deficits in BACE1 knock-outs are directly attributable to lacking APP processing is unclear. Previous studies suggest that generation of excess Aβ depresses excitatory synaptic transmission, mainly by postsynaptic removal of AMPA receptors and loss of synapses (Hsieh et al., 2006; Priller et al., 2006; Ting et al., 2007). These results would predict that lacking Aβ production, as in BACE1 knock-outs, would cause a postsynaptic increase in AMPA receptor function, not a decrease in presynaptic function as observed in our studies. However, we cannot rule out the possibility of gain-of-function in the Aβ overexpression studies.

Another possibility is that the presynaptic effects of BACE1 knock-out may be from abnormal processing of substrates other than APP. It is now known that BACE1 can also cleave APP-like proteins (Li and Südhof, 2004), β subunits of voltage-gated Na^+ channel (Wong et al., 2005; Kim et al., 2007), and neuregulin-1 (NRG1) (Hu et al., 2006; Willem et al., 2006). Regulation of the latter two substrates is particularly interesting. The β2 subunit of Na^+ channel is critical for plasma membrane expression of functional Na^+ channels (Schmidt and Catterall, 1986), which are essential for action potential generation. However, overexpressing BACE1 actually decreases the density of functional Na^+ channels (Kim et al., 2007); hence, it cannot directly account for the observed reduction in presynaptic release in the BACE1 knock-outs. Potential regulation of NRG1 by BACE1 was discovered from observations that BACE1 knock-outs display a hypomyelination phenotype with a correlated accumulation of full-length NRG1 and a significant loss of NRG1 cleavage products (Hu et al., 2006; Willem et al., 2006). Recently, we demonstrated that the lack of NRG1 processing in BACE1 knock-outs reduces postsynaptic function of ErbB4, a receptor for NRG1 (Savonenko et al., 2008). NRG1/ErbB4 signaling has been suggested to regulate synaptic function and plasticity, mainly via regulation of postsynaptic glutamate receptors (Huang et al., 2000; Gu et al., 2005; Li et al., 2007). Nevertheless, abnormal processing of NRG1 may also affect presynaptic release by regulating the expression of nicotinic acetylcholine receptor (nAchR) subunit α7 (Liu et al., 2001), which allows Ca^{2+} influx (Séguéla et al., 1993). Indeed, presynaptic nAchRs can increase glutamate release (McGehee et al., 1995; Gray et al., 1996; Maggi et al., 2003), likely via the α7 containing nAchRs (Le Magueresse et al., 2006). These results suggest that lacking NRG1 cleavage, as in BACE1 knock-outs, would reduce presynaptic release. Whether this is the case for mossy fiber synapses is unclear (Vogt and Regehr, 2001).

Our results indicate that a complete inhibition of BACE1 activity is deleterious for neuronal function, especially at the mossy fiber synapses in CA3 compared with Schaffer collateral inputs in CA1. This suggests that mossy fiber dysfunction may have had a larger impact on the behavioral phenotypes seen in the BACE1 knock-outs (Harrison et al., 2003; Laird et al., 2005; Savonenko et al., 2008). We demonstrate that signaling downstream of presynaptic Ca^{2+} is intact in BACE1 knock-outs. Therefore, we were able to restore mossy fiber LTP in the BACE1 knock-outs by simply increasing extracellular Ca^{2+} concentration during LTP induction. This has significant clinical implications because it suggests that means to enhance presynaptic Ca^{2+} will circumvent synaptic deficits, and afterhaps alleviate the behavioral phenotypes, associated with inhibiting BACE1 activity.

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