Published in final edited form as:

Neurobiol Learn Mem. 2009 July ; 92(1): 120–123. doi:10.1016/j.nlm.2009.02.006.

Autophosphorylation of α CaMKII downregulates excitability of CA1 pyramidal neurons following synaptic stimulation

Evgeny A. Sametsky^a, John F. Disterhoft^a, and Masuo Ohno^{b,*}

^aDepartment of Physiology, Northwestern University Feinberg School of Medicine, Chicago, IL 60611-3008, USA

^bCenter for Dementia Research, Nathan Kline Institute, New York University School of Medicine, Orangeburg, NY 10962, USA

Abstract

It has been well documented that α -calcium/calmodulin-dependent protein kinase II (α CaMKII) is central to synaptic plasticity such as long-term potentiation, an activity-dependent strengthening of synapses that is thought to underlie certain types of learning and memory. However, the mechanisms by which α CaMKII may regulate neuronal excitability remain unclear. Here, we report that α CaMKII knock-in mice with a targeted T286A point mutation that prevents its autophosphorylation (α CaMKII^{T286A}) showed increased excitability of CA1 pyramidal neurons compared with wild-type controls, as measured by a decrease in the slow component of post-burst afterhyperpolarization (sAHP) following high-frequency stimulation of Schaffer collateral afferent fibers. In contrast, AHP was indistinguishable between α CaMKII^{T286A} and wild-type mice when it was evoked by somatic current injections, indicating that the hyperexcitability is observed specifically in response to synaptic stimulation in this mutant. Taken together, our results suggest that α CaMKII functions to downregulate CA1 neuron excitability following synaptic stimulation, presumably supporting the functionally adaptive modulation of excitability during hippocampal learning or providing a negative feedback mechanism that would prevent neurons from becoming hyperexcitable and promote network stability.

Keywords

α -calcium/calmodulin-dependent protein kinase II; T286A; excitability; afterhyperpolarization (AHP); hippocampus; CA1; Schaffer collateral

α -Calcium/calmodulin-dependent protein kinase II (α CaMKII) is highly abundant in excitatory principal neurons in forebrain structures such as the hippocampus, where it makes up ~2% of the total protein and is a major constituent of the postsynaptic density (Kennedy, 2000). A key feature of α CaMKII is that autophosphorylation occurs at threonine-286 of the α CaMKII protein in response to Ca^{2+} influx and switches the kinase into a Ca^{2+} /calmodulin-independent or autonomously active state (Hudmon and Schulman, 2002). The autophosphorylation is a prerequisite event for changes in synaptic strength such as long-

*Corresponding author. Center for Dementia Research, Nathan Kline Institute, New York University School of Medicine, 140 Old Orangeburg Road, Orangeburg, NY 10962, USA. Tel.: +1 845 398 6599; Fax: +1 845 398 5422., mohno@nki.rfmh.org (M. Ohno).

term potentiation (LTP), a cellular mechanism for learning and memory, since a targeted point mutation at residue-286 in the mouse α CaMKII gene in which threonine is replaced by alanine (T286A) prevents autophosphorylation at this site, resulting in the block of NMDA receptor-dependent hippocampal LTP and learning failures (Giese et al., 1998; Irvine et al., 2005; Need and Giese, 2003; Ohno et al., 2002; Ohno et al., 2006; Ohno et al., 2005).

In addition, alteration of intrinsic neuronal excitability occurs in animals that are trained and learn hippocampus-dependent tasks, representing an important cellular correlate of learning (for review, see Disterhoft and Oh, 2006). For example, we have demonstrated that increases in CA1 pyramidal neuron excitability, as evidenced by a decrease in the post-burst afterhyperpolarization (AHP), are observed during trace eyeblink conditioning and water maze learning across various animal species (Disterhoft et al., 1986; Kuo et al., 2008; Moyer et al., 1996; Oh et al., 2003; Ohno et al., 2006). It is reasonable to suppose that the neuronal excitability changes may be closely coordinated with synaptic alterations during hippocampal memory encoding. In contrast to the well-documented roles of autophosphorylation of α CaMKII and its subsequent persistent activation in synaptic plasticity (Irvine et al., 2006; Lisman et al., 2002), it remains unclear how this kinase may contribute to the regulation of neuron excitability during synaptic stimulation. To address this question, we analyzed the AHP in hippocampal CA1 neurons following Schaffer collateral afferent stimulation in the autophosphorylation-deficient α CaMKII^{T286A} knock-in mice.

The heterozygous α CaMKII^{T286A} population (Giese et al., 1998) was backcrossed more than 15 generations into the C57BL/6N background from the original 129/B6 background. Homozygous α CaMKII^{T286A} mutant mice and wild-type control littermates obtained by intercrosses of heterozygotes were used for the experiments. At 3–4 weeks postnatally, the mice were weaned and genotyping was performed by PCR analysis of tail DNA. All experiments were done blind with respect to the genotype of the mice and were conducted with the approval of the Northwestern University or Nathan Kline Institute Animal Care and Use Committee.

After brains were removed from mice following decapitation under deep halothane anesthesia, transverse hippocampal slices (300 μ m thick) were prepared using a vibratome (VT 1000, Leica Microsystems, Wetzlar, Germany) and were maintained in an artificial cerebral spinal fluid (aCSF)-filled holding chamber at room temperature for at least 1 h. The standard aCSF contained (in mM) 124 NaCl, 3 KCl, 2.4 CaCl₂, 2 MgCl₂, 1.25 NaH₂PO₄, 26 NaHCO₃ and 10 D-glucose, and was equilibrated with 95% O₂ and 5% CO₂. The concentration of CaCl₂ was decreased to 1.4 mM in slicing solution. Picrotoxin (0.25 mM) was added to suppress GABAergic synaptic inhibition during recording. A surgical cut between CA3 and CA1 was made before slices were transferred to a submerged glass-bottom recording chamber mounted onto the stage of an upright microscope (DM-LFS, Leica Microsystems). The chamber was constantly perfused with oxygenated aCSF (2 ml/min) at 35 °C. Individual CA1 pyramidal cells were visualized using a long-distance water-immersion (X40) objective and infrared differential interference contrast (IR-DIC) illumination. Whole-cell current clamp recordings were made from CA1 pyramidal neurons with membrane potentials maintained at –68 mV, as described previously (Ohno et al.,

2006; Ohno et al., 2004). Patch electrodes (4–5 M Ω) were filled with an intracellular solution containing (in mM) 130 potassium methylsulfate, 10 KCl, 10 HEPES, 2 K₂-ATP, 1 MgCl₂, (pH 7.3–7.4, osmolarity 290 $\pm$ 10 mOsm). The AHP was evoked by applying depolarization pulses (2 ms in duration, 50 Hz) into the soma or Schaffer collateral stimulation (100- μ s pulses at 50 Hz) through a bipolar cluster electrode (FHC, Bowdoin, USA) that was placed in the stratum radiatum layer of CA1 area. In both protocols to trigger the AHP, we used the suprathreshold stimulus intensity so that a train of 2–30 stimuli could consistently elicit a burst of 2–30 corresponding action potentials. A total of ten AHP measurements were made for each current injection and synaptic stimulation that evoked 2, 5, 10, 15, 20, 25 or 30 spikes from each neuron at 20-s intervals. The AHP was measured by the amplitudes at peak and 1 s after pulse offset. The significance of differences between the groups was determined by a two-way ANOVA with repeated measures, which was followed by Student's *t*-test for the comparison of each point. The level of significance was set for *p* value less than 0.05, and all data were reported as the mean $\pm$ SEM.

We first tested the post-burst AHP evoked by direct current injections into CA1 pyramidal neurons (Fig. 1). As the number of spikes increased, the amplitude of the slow AHP (sAHP) measured at 1 s after the end of the pulse increased similarly in α CaMKII^{T286A} mutant and wild-type control mice ($F_{6,150} = 98.93$; $p < 0.05$). The analysis revealed neither a significant main effect of group ($F_{1,25} = 0.08$; $p > 0.05$) nor a significant interaction between genotype and the number of spikes ($F_{6,150} = 0.41$; $p > 0.05$). Furthermore, no difference was found in peak amplitudes of the AHP between both groups. Therefore, α CaMKII^{T286A} mice exhibited an AHP that was comparable to that of wild-type mice when the AHP was evoked by depolarization current injections into the soma, indicating that the baseline somatic membrane excitability was normal in CA1 pyramidal neurons of α CaMKII^{T286A} mutants.

We next compared the post-burst AHP in CA1 neurons triggered by high-frequency simulation of Schaffer collateral afferent fibers (Fig. 2). While the sAHP increased with the number of spikes in both groups ($F_{6,96} = 142.40$; $p < 0.05$), α CaMKII^{T286A} mice showed decreased levels of sAHP compared with wild-type controls as indicated by a significant main effect of group ($F_{1,16} = 7.42$; $p < 0.05$) and a significant interaction between genotype and the number of spikes ($F_{6,96} = 3.22$; $p < 0.05$). Post-hoc Student's *t*-test revealed that significantly smaller levels of sAHP were observed in α CaMKII^{T286A} mice from 5- to 30-spike protocols ($p < 0.05$) except for the point of 25-spike-evoked sAHP ($p = 0.07$). Therefore, CA1 pyramidal neurons of α CaMKII^{T286A} mutants specifically exhibited higher levels of excitability, as detected by reductions in sAHP, than those of wild-type control mice when synaptic stimulation was recruited to induce the post-burst AHP. In contrast, the peak amplitude of the AHP was indistinguishable between both groups throughout 2–30-spike synaptic stimulation protocols, implying that apamin-sensitive SK channels that mostly underlie the medium AHP (Disterhoft and Oh, 2006) may not be involved in the α CaMKII-dependent regulation of AHP. Through the patch-clamp recordings, we observed no significant differences between mutant and wild-type control mice in cell parameters such as input resistance (α CaMKII^{T286A}, 124.5 $\pm$ 10.0 M Ω ; wild-type, 113.7 $\pm$ 8.2 M Ω), access resistance (α CaMKII^{T286A}, 21.3 $\pm$ 1.0 M Ω ; wild-type, 21.4 $\pm$ 1.3 M Ω), time constant

(α CaMKII^{T286A}, 23.9 ± 1.3 msec; wild-type, 22.3 ± 0.8 msec) and capacitance (α CaMKII^{T286A}, 82.7 ± 5.1 pF; wild-type, 83.8 ± 5.5 pF).

The increase in the autophosphorylated or autonomously active form of CaMKII is a crucial molecular step that enables hippocampus-dependent memory formation such as water maze and contextual fear learning (Atkins et al., 1998; Tan and Liang, 1996). Therefore, it is important to explore the functional interactions between CaMKII autophosphorylation and K⁺ channels so that we can fully understand the mechanisms by which CaMKII signaling may contribute to learning processing by modulating neuron excitability. Varga et al. (2004) previously reported that introduction of constitutively active CaMKII increases A-type K⁺ current in cultured CA1 pyramidal neurons, suggesting that increased CaMKII activity leads to decreased hippocampal neuronal excitability. Our present study demonstrated that autophosphorylation-deficient α CaMKII^{T286A} knock-in mice show increased excitability of CA1 neurons, as assessed by reduced levels of sAHP, following high-frequency stimulation of Schaffer collateral afferents. Consistent with our results, a theta-burst pairing, which consists of subthreshold synaptic stimulation paired with backpropagating action potentials at theta frequency, results in overall reductions in CA1 excitability through CaMKII autophosphorylation-dependent upregulation of the hyperpolarization-activated cation current (I_h) in hippocampal slices from adult rats (Fan et al., 2005). Taken collectively, it is likely that α CaMKII autophosphorylation and the subsequent persistent activation of this kinase function to downregulate CA1 neuron excitability following synaptic stimulation, via different mechanisms but in the same direction.

Interestingly, in our experiments, the hyperexcitability was specific to synaptic activation in CA1 neurons of α CaMKII^{T286A} mice and sAHP elicited by intracellular current injections did not differ between mutants and wild-type controls. What mechanisms may account for this difference? Ca²⁺ influx in pyramidal cells primarily occurs in dendrites after postsynaptic depolarization and involves NMDA glutamatergic receptors, voltage-gated calcium channels (VGCC) and calcium-induced calcium release (CICR) from internal calcium stores (Berridge, 1998). Consequently, we found that the sAHP amplitude was twice larger with synaptic stimulation as compared to sAHP triggered with somatic depolarization. While the sAHP increased with the number of action potential spikes in both protocols, the larger sAHP was always evoked with synaptic stimulation. This suggests that even a strong repetitive somatic depolarization may not saturate sAHP in CA1 pyramidal neurons and activation of sAHP with synaptic stimulation is more physiological. Thus, the key role of sAHP is to counteract a synchronized synaptic excitatory input that is able to propagate along apical dendrites and generate action potentials. Indeed, the Schaffer collateral stimulation-induced sAHP is mediated by evoked glutamate release, while sAHP following direct depolarization of the soma occurs independent of neurotransmitters. It should be noted that NMDA receptor functions, as measured by the amplitude or voltage dependence of NMDA currents, are normal in CA1 neurons of α CaMKII^{T286A} mice (Giese et al., 1998), excluding the possibility that reduced levels of Ca²⁺ influx through NMDA receptors may result in the changes in calcium-dependent sAHP following synaptic stimulation in this mutant. A plausible mechanism is that α CaMKII specifically activated via postsynaptic glutamate receptor stimulation may directly phosphorylate or indirectly

modulate potassium channels responsible for sAHP and upregulate the channel activity. It seems reasonable to speculate that such α CaMKII-dependent regulatory pathways may be omitted if sAHP is evoked by somatic current injections. Alternatively, α CaMKII regulation of the post-burst AHP might be an indirect result of the phosphorylation of or α CaMKII binding to VGCC that results in prolongation of Ca^{2+} influx through these channels (Jiang X et al., 2008; Lee et al., 2006; Welsby PJ et al., 2003). Further studies will be needed to fully understand the molecular machinery that links synaptic α CaMKII and the regulation of neuron excitability through sAHP channels.

Among several plasticity-related and Ca^{2+} -dependent protein kinases that are involved in learning and memory, extracellular signal-regulated kinase (ERK), PKC and PKA have been demonstrated to increase CA1 neuron excitability through downregulation of dendritic K^{+} channels (Hoffman and Johnston, 1998; Yuan et al., 2002). In fact, these kinases are critically involved in learning-related increases in neuronal excitability since learning occludes kinase-mediated AHP reductions and applications of kinase inhibitors abolish learning-induced long-lasting reductions in AHP (Cohen-Matsliah et al., 2007; Oh et al., 2009; Seroussi et al., 2002). In contrast, given that CaMKII represents a negative modulator of CA1 neuron excitability following synaptic stimulation, how can this mechanism be involved in the modulation of excitability with relevance to learning and memory? Our previous study demonstrated that the post-burst sAHP evoked by depolarizing current injections into CA1 pyramidal cells was reduced to similar levels in both α CaMKII^{T286A} mutants and wild-type controls after spatial training in the water maze. Therefore, it is apparent that α CaMKII signaling is not responsible for increasing excitability during hippocampal learning. Interestingly, whereas wild-type mice reduced sAHP or increased their CA1 neuron excitability in a learning-specific manner, α CaMKII^{T286A} mice devoid of spatial learning abilities did so as a consequence of swim performance by itself (rather than learning) in the absence of the escape platform (Ohno et al., 2006). Together with our present results, it seems reasonable to speculate that α CaMKII signaling may be important for suppressing a learning-unrelated component of excitability changes in response to synaptic activation during behavioral training and thereby optimizing the specificity of CA1 pyramidal neurons to undergo increases in excitability associated with learning. It is also plausible that α CaMKII may represent a negative feedback mechanism that would normalize neuronal excitability and thus stabilize hippocampal networks following synaptic stimulation once memory is encoded. Further experiments with synaptically evoked post-burst AHP could give better understanding how α CaMKII is involved in learning-associated changes in cell excitability. In either case, our findings support the idea that α CaMKII autophosphorylation may provide a crucial step for CA1 neurons to adaptively modulate the sAHP and excitability in the context of learning.

In summary, the present findings suggest that α CaMKII, a major synaptic protein, plays a role not only in mediating synaptic plasticity but also in suppressing neuron excitability following synaptic activation, which would support coordinated neuronal outputs by consolidating learning-specific adaptive alterations of excitability during memory encoding.

Acknowledgments

This work was supported by National Institutes of Health grants R01 MH067251 (M.O.) and R37 AG08796 (J.F.D.).

References

- Atkins CM, Selcher JC, Petraitis J, Trzaskos J, Sweatt J. The MAPK cascade is required for mammalian associative learning. *Nat Neurosci.* 1998; 1:602–609. [PubMed: 10196568]
- Berridge MJ. Neuronal calcium signaling. *Neuron.* 1998; 21:13–26. [PubMed: 9697848]
- Cohen-Matsliah SI, Brosh I, Rosenblum K, Barkai E. A novel role for extracellular signal-regulated kinase in maintaining long-term memory-relevant excitability changes. *J Neurosci.* 2007; 27:12584–12589. [PubMed: 18003837]
- Disterhoft JF, Coulter DA, Alkon DL. Conditioning-specific membrane changes of rabbit hippocampal neurons measured *in vitro*. *Proc Natl Acad Sci USA.* 1986; 83:2733–2737. [PubMed: 3458232]
- Disterhoft JF, Oh MM. Learning, aging and intrinsic neuronal plasticity. *Trends Neurosci.* 2006; 29:587–599. [PubMed: 16942805]
- Fan Y, Fricker D, Brager DH, Chen X, Lu HC, Chitwood RA, Johnston D. Activity-dependent decrease of excitability in rat hippocampal neurons through increases in I_h . *Nat Neurosci.* 2005; 8:1542–1551. [PubMed: 16234810]
- Giese KP, Fedorov NB, Filipkowski RK, Silva AJ. Autophosphorylation at Thr²⁸⁶ of the α calcium-calmodulin kinase II in LTP and learning. *Science.* 1998; 279:870–873. [PubMed: 9452388]
- Hoffman DA, Johnston D. Downregulation of transient K^+ channels in dendrites of hippocampal CA1 pyramidal neurons by activation of PKA and PKC. *J Neurosci.* 1998; 18:3521–3528. [PubMed: 9570783]
- Hudmon A, Schulman H. Neuronal Ca^{2+} /calmodulin-dependent protein kinase II: the role of structure and autoregulation in cellular function. *Annu Rev Biochem.* 2002; 71:473–510. [PubMed: 12045104]
- Irvine EE, Vernon J, Giese KP. α CaMKII autophosphorylation contributes to rapid learning but is not necessary for memory. *Nat Neurosci.* 2005; 8:411–412. [PubMed: 15778710]
- Irvine EE, von Herten LS, Plattner F, Giese KP. α CaMKII autophosphorylation: a fast track to memory. *Trends Neurosci.* 2006; 29:459–465. [PubMed: 16806507]
- Jiang X, Lautermilch NJ, Watari H, Westenbroek RE, Scheuer T, Catterall WA. Modulation of $CaV2.1$ channels by Ca^{2+} /calmodulin-dependent protein kinase II bound to the C-terminal domain. *Proc Natl Acad Sci USA.* 2008; 105:341–346. [PubMed: 18162541]
- Kennedy MB. Signal-processing machines at the postsynaptic density. *Science.* 2000; 290:750–754. [PubMed: 11052931]
- Kuo AG, Lee G, McKay BM, Disterhoft JF. Enhanced neuronal excitability in rat CA1 pyramidal neurons following trace eyeblink conditioning acquisition is not due to alterations in I M. *Neurobiol Learn Mem.* 2008; 89:125–133. [PubMed: 17703960]
- Lee T-S, Karl R, Moosmang S, Lenhardt P, Klugbauer N, Hofmann F, Kleppisch T, Welling A. Calmodulin kinase II is involved in voltage-dependent facilitation of the L-type $CaV1.2$ calcium channel: Identification of the phosphorylation sites. *J Biol Chem.* 2006; 281:25560–25567. [PubMed: 16820363]
- Lisman J, Schulman H, Cline H. The molecular basis of CaMKII function in synaptic and behavioural memory. *Nat Rev Neurosci.* 2002; 3:175–190. [PubMed: 11994750]
- Moyer JR Jr, Thompson LT, Disterhoft JF. Trace eyeblink conditioning increases CA1 excitability in a transient and learning-specific manner. *Journal of Neuroscience.* 1996; 16:5536–5546. [PubMed: 8757265]
- Need AC, Giese KP. Handling and environmental enrichment do not rescue learning and memory impairments in α CamKII^{T286A} mutant mice. *Genes Brain Behav.* 2003; 2:132–139. [PubMed: 12931786]
- Oh MM, Kuo AG, Wu WW, Sametsky EA, Disterhoft JF. Watermaze learning enhances excitability of CA1 pyramidal neurons. *J Neurophysiol.* 2003; 90:2171–2179. [PubMed: 12815013]

- Oh MM, McKay BM, Power JM, Disterhoft JF. Learning-related postburst afterhyperpolarization reduction in CA1 pyramidal neurons is mediated by protein kinase A. *Proc Natl Acad Sci USA*. 2009; 106:1620–1625. [PubMed: 19164584]
- Ohno M, Frankland PW, Silva AJ. A pharmacogenetic inducible approach to the study of NMDA/ α CaMKII signaling in synaptic plasticity. *Curr Biol*. 2002; 12:654–656. [PubMed: 11967152]
- Ohno M, Sametsky EA, Silva AJ, Disterhoft JF. Differential effects of α CaMKII mutation on hippocampal learning and changes in intrinsic neuronal excitability. *Eur J Neurosci*. 2006; 23:2235–2240. [PubMed: 16630070]
- Ohno M, Sametsky EA, Younkin LH, Oakley H, Younkin SG, Citron M, Vassar R, Disterhoft JF. BACE1 deficiency rescues memory deficits and cholinergic dysfunction in a mouse model of Alzheimer's disease. *Neuron*. 2004; 41:27–33. [PubMed: 14715132]
- Ohno M, Tseng W, Silva AJ, Disterhoft JF. Trace eyeblink conditioning requires the hippocampus but not autophosphorylation of α CaMKII in mice. *Learn Mem*. 2005; 12:211–215. [PubMed: 15897256]
- Seroussi Y, Brosh I, Barkai E. Learning-induced reduction in post-burst afterhyperpolarization (AHP) is mediated by activation of PKC. *Eur J Neurosci*. 2002; 16:965–969. [PubMed: 12372033]
- Tan SE, Liang KC. Spatial learning alters hippocampal calcium/calmodulin-dependent protein kinase II activity in rats. *Brain Res*. 1996; 711:234–240. [PubMed: 8680867]
- Varga AW, Yuan LL, Anderson AE, Schrader LA, Wu GY, Gatchel JR, Johnston D, Sweatt JD. Calcium-calmodulin-dependent kinase II modulates Kv4.2 channel expression and upregulates neuronal A-type potassium currents. *J Neurosci*. 2004; 24:3643–3654. [PubMed: 15071113]
- Welsby PJ, Wang H, Wolfe JT, Colbran RJ, Johnson ML, Barrett PQ. A mechanism for the direct regulation of T-type calcium channels by Ca^{2+} /calmodulin-dependent kinase II. *J Neurosci*. 2003; 23:10116–10121. [PubMed: 14602827]
- Yuan LL, Adams JP, Swank M, Sweatt JD, Johnston D. Protein kinase modulation of dendritic K^{+} channels in hippocampus involves a mitogen-activated protein kinase pathway. *J Neurosci*. 2002; 22:4860–4868. [PubMed: 12077183]

Fig. 1.

The $\alpha\text{CaMKII}^{\text{T286A}}$ mutation does not affect post-burst AHP following depolarizing current injections into CA1 pyramidal neurons. (A) Representative recordings of the AHP from a wild-type slice in response to 2–30-spike pulses (A_1), and those from wild-type and $\alpha\text{CaMKII}^{\text{T286A}}$ slices in response to 20-spike pulses (A_2). (B) AHP was evoked by applying 2–30 depolarization pulses at 50 Hz, and the slow component of AHP (sAHP) was measured by amplitudes at 1 s after pulse offset. Data are presented as mean $\pm$ SEM. The amplitude of

sAHP was indistinguishable between α CaMKII^{T286A} mutants ($n = 15$) and wild-type controls ($n = 12$).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Fig. 2.

The $\alpha\text{CaMKII}^{\text{T286A}}$ mutation reduces post-burst AHP in CA1 pyramidal neurons following Schaffer collateral afferent stimulation. (A) Representative recordings of the AHP from a wild-type slice in response to 2–30-spike pulses (A₁), and those from wild-type and $\alpha\text{CaMKII}^{\text{T286A}}$ slices in response to 20 pulses (A₂). Note that the slow component of AHP (sAHP) was specifically reduced in $\alpha\text{CaMKII}^{\text{T286A}}$ mice without changes in the peak amplitude of AHP. (B) AHP was evoked by applying 2–30 suprathreshold synaptic stimuli at 50 Hz that reliably induced the corresponding number of action potentials, and the sAHP

was measured by amplitudes at 1 s after pulse offset. Data are presented as mean $\pm$ SEM. The amplitude of sAHP was significantly smaller in α CaMKII^{T286A} mutants ($n = 10$) as compared with wild-type controls ($n = 8$). * $p < 0.05$ versus wild-type controls.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript