Brief Communications

Acid-Sensing Ion Channel-1a Is Not Required for Normal Hippocampal LTP and Spatial Memory

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Acid-sensing ion channel-1a (ASIC1a) is localized in brain regions with high synaptic density and is thought to contribute to synaptic plasticity, learning, and memory. A prominent hypothesis is that activation of postsynaptic ASICs promotes depolarization, thereby augmenting *N*-methyl-D-aspartate receptor function and contributing to the induction of long-term potentiation (LTP). However, evidence for activation of postsynaptic ASICs during neurotransmission has not been established. Here, we re-examined the role of ASIC1a in LTP in the hippocampus using pharmacological and genetic approaches. Our results showed that a tarantula peptide psalmotoxin, which profoundly blocked ASIC currents in the hippocampal neurons, had no effect on LTP. Similarly, normal LTP was robustly generated in ASIC1a-null mice. A further behavioral analysis showed that mice lacking ASIC1a had normal performance in hippocampus-dependent spatial memory. In summary, our results indicate that ASIC1a is not required for hippocampal LTP and spatial memory. We therefore propose that the role of ASIC1a in LTP and spatial learning should be reassessed.

Introduction

Acid-sensing ion channels (ASICs), members of the degenerin/epithelial Na^+ channel superfamily, are widely distributed in the mammalian nervous system (Waldmann et al., 1997) and have been implicated in learning and memory (Wemmie et al., 2002; Wemmie et al., 2003). To date, four genes (*ASIC1–ASIC4*) have been identified and they encode six isoforms (ASIC1a, ASIC1b, ASIC2a, ASIC2b, ASIC3, and ASIC4) through alternative splicing (Bässler et al., 2001; review by Krishtal, 2003). At the least, ASIC1a, ASIC2a, and ASIC2b are expressed in the brain and the spinal cord (Waldmann et al., 1997; Baron et al., 2002; Alvarez de la Rosa et al., 2003; Baron et al., 2008). Expression of homomeric ASIC1a, heteromeric ASIC1a/2a, and ASIC1a/2b channels are found in hippocampal neurons (Baron et al., 2002; Askwith et al., 2004; Weng et al., 2010; Sherwood et al., 2011). Subunit ASIC1a is thought to be an obligatory subunit because ASIC-like currents are not detectable in ASIC1a-null neurons (Wemmie et al., 2002; Wemmie et al., 2003). Crystal structure of the chicken homomeric ASIC1a channel suggests that three subunits are required to form a functional channel (Jasti et al., 2007).

Mice lacking *ASIC1a* gene display deficits in hippocampus- and amygdala-dependent memories and behaviors (Wemmie et al., 2002; Wemmie et al., 2003). Furthermore, hippocampal long-term potentiation (LTP) was found to be strikingly impaired in ASIC1a-null mice (Wemmie et al., 2002). Although the functional relevance of ASIC1a in regulating synaptic transmission remains elusive, Wemmie et al. (2002) suggested that activation of postsynaptic ASICs promotes membrane depolarization, thereby facilitating *N*-methyl-D-aspartate receptor function and contributing to LTP. Evidence in support of this hypothesis primarily comes from the experiment that LTP was induced in low Mg^{2+} medium in ASIC1a knockout (KO) mice (Wemmie et al., 2002). However, this hypothesis is paradoxical because evidence for the presence of postsynaptic ASIC-like currents during neurotransmission has not been established (Alvarez de la Rosa et al., 2003; Krishtal, 2003; Wemmie et al., 2006).

Here we attempted to revisit the role for ASIC1a in hippocampal LTP using two independent approaches. First, psalmotoxin 1 (PcTX1), a peptide extracted from the venom of the South American tarantula *Psalmopoeus cambridgei*, is so far the best-known selective inhibitor of ASIC1a (Escoubas et al., 2000; Baron et al., 2002; Chen et al., 2005) and ASIC1a/2b channels (Sherwood et al., 2011). We demonstrated that PcTX1 largely inhibited ASIC-like currents but did not impair LTP in the hippocampus. Second, we tested the essential role of ASIC1a in LTP with ASIC1a-null

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mice. Consistent with the acute blockade of ASICs, normal LTP was generated in ASIC1a-null mice, indicating that ASIC1a is not essential for LTP.

Materials and Methods

Preparation of hippocampal slices. Transverse hippocampal slices (300–400 μm thick) were prepared from male Sprague Dawley rats (14–21 d old) and mice of either sex (2–4 months old) using a microslicer (DTK-1000, Dosaka). Floxed ASIC1a mice on C57BL/6 genetic background were maintained in the National Yang-Ming University (NYMU). Briefly, *ASIC1a*$^{flx/+}$ mice on mixed 129/C57BL/6 genetic background were backcrossed to C57BL/6 mice for at least eight generations, and the resulting *ASIC1a*$^{flx/+}$ heterozygous mice were intercrossed to generate *ASIC1a*$^{flx/flx}$ mice. To selectively delete *ASIC1a* gene in the nervous system, *ASIC1a*$^{flx/flx}$ mutants were crossed with the Nestin–Cre transgenic mice that expressed Cre recombinase under the control of a rat Nestin promoter and the nervous system-specific enhancer (Tronche et al., 1999). This caused recombination between the *loxP* sites and loss of the intervening genomic sequence (Fig. 2*A*) in their offspring. Animals were sacrificed by decapitation in agreement with national and institutional guidelines, and all procedures were approved by the Animal Care and Use Committee of the NYMU. Slices were sectioned in ice-cold artificial cerebrospinal fluid (ACSF) containing (in mM): 125 NaCl, 25 $NaHCO_3$, 1.25 NaH_2PO_4, 2.5 KCl, 25 glucose, 2 $CaCl_2$, and 1 $MgCl_2$. Following sectioning, slices were incubated in a holding chamber filled with the oxygenated (saturated with 95% O_2/5% CO_2) ACSF at 34°C for 25 min, and then at room temperature until used. During experiments, an individual slice was transferred to a submerged chamber and was continuously superfused with oxygenated ACSF at a rate of 5–7 ml/min.

Electrophysiology. Patch pipettes for whole-cell recordings were pulled from borosilicate glass tubing (outer diameter, 1.5 mm; inner diameter, 0.86 mm; Harvard Apparatus) and heat-polished before use. The pipette resistance ranged from 5 to 10 MΩ. Experiments were performed under visual control using an infrared differential interference contrast microscope (BX51WI, Olympus). Whole-cell patch-clamp recordings of hippocampal neurons in acute brain slices were made using a Multiclamp 700B amplifier (Molecular Devices). H^+-activated currents were induced by focal puffs of acidic solutions to the somata of recorded neurons using a Picospritzer (Parker) in the presence of synaptic blockers kynurenic acid and gabazine or by fast application of H^+ to the nucleated patches as described previously (Chu et al., 2010; Lin et al., 2010; Weng et al., 2010). The HEPES-buffered Na^+-rich external solution in the control barrel contained (in mM): 135 NaCl, 2.5 KCl, 0.5 $CaCl_2$, 1 $MgCl_2$ and 10 HEPES; pH was adjusted to 7.4 with *N*-methyl-D-glucamine (NMDG). To activate ASIC currents, we applied 2-(*N*-morpholino)ethanesulfonic acid (MES)-buffered Na^+-rich external solution containing (in mM): 135 NaCl, 2.5 KCl, 0.5 $CaCl_2$, 1 $MgCl_2$ and 10 MES, adjusted to desired pH with NMDG. Pipette capacitance was compensated. Series resistance (10–20 MΩ) was fully compensated in current-clamp recording and to 80% in voltage-clamp configuration.

Field excitatory postsynaptic potentials (fEPSPs) in the presence of the GABA receptor type A ($GABA_AR$) antagonist gabazine (1 μM) were recorded in the CA1 area with ASCF-filled glass pipettes (1–2 MΩ). Basal fEPSPs were evoked by a brief pulse (0.1–0.2 ms) of either constant voltage or current delivered by stimulus isolation unit (ISO-Flex, A.M.P.I.) every 30 s with a tungsten bipolar electrode (Microprobe) positioned in the stratum radiatum. The stimulation electrode was 200–300 μm away from the recording pipette. Synaptic strength was quantified as the initial slope of fEPSP. Baseline responses were collected with a stimulation intensity that yielded 30–50% of the maximal response. Slices displaying unstable baseline recording were discarded. After obtaining a stable baseline for 20 min, LTP was induced with the same stimulating strength used during baseline recording by 1–4 trains of high-frequency stimulation (HFS) (100 pulses at 100 Hz) with 20 s intervals between trains. Signals were filtered at 2 or 4 kHz (field and whole-cell recordings, respectively) and digitized at 10 kHz using the Digidata 1440 (Molecular Devices); data acquisition and pulse generation were performed using pClamp 10.2 (Molecular Devices). Recordings were made at 24 ± 1°C. The ASIC antagonist, PcTX1 (30 nM) was present throughout the duration of the LTP experiment (70–80 min). LTP experiments using PcTX1 were interleaved with control experiments. All data from transgenic mice were obtained in blind coded experiments in which the investigators who obtained the data were unaware of the specific genotype.

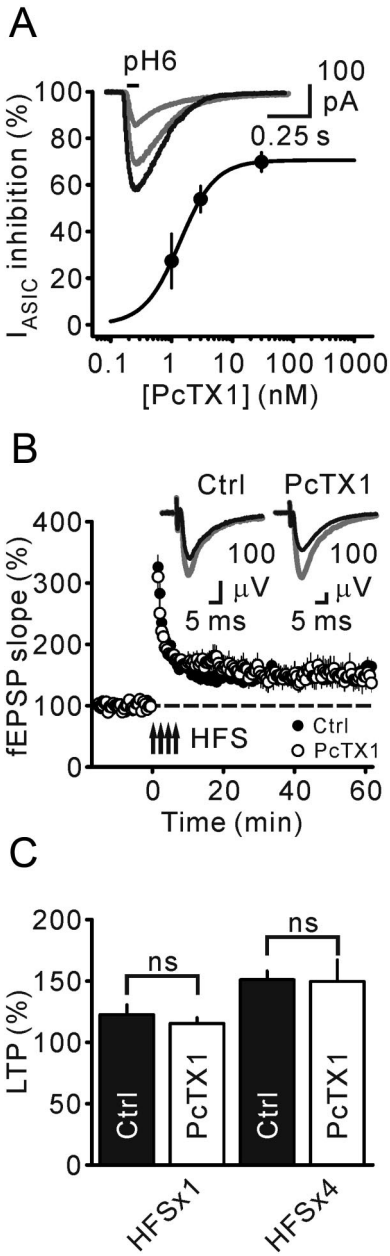

Figure 1. PcTX1, a selective inhibitor of ASIC1a and ASIC1a/2b channels, had no effect on LTP at SC-CA1 synapses. ***A***, Inset, Representative ASIC-like current traces in the control (Ctrl, black) and after application of 1 and 30 nM PcTX1 (gray). Data were fitted to a single Hill equation with IC_{50} = 1.36 nM (Hill coefficient, 1.5). Each point represented the average from 6–13 experiments. ***B***, High-frequency stimulation (four trains)-induced LTP was not impaired by high concentration of PcTX1 (30 nM, n = 6, 5 animals) as compared with the Ctrl (n = 7, 7 animals). ***C***, Summary of LTP induced by different induction protocols in Ctrl (HFS × 1, n = 5, 5 animals; HFS × 4, n = 7, 7 animals) and in the presence of PcTX1 (HFS × 1, n = 6, 5 animals; HFS × 4, n = 6, 5 animals); ns, not significantly different.

Solutions and drugs. The intracellular solution for recording pipettes consisted of (in mM): 135 K-gluconate, 20 KCl, 0.1 EGTA, 2 $MgCl_2$, 4 Na_2ATP, 10 HEPES, 0.3 Na_3GTP, pH adjusted to 7.3 with KOH. Kynurenic acid was from Sigma and Ascent Scientific; gabazine was from Tocris Bioscience and Ascent Scientific. Solutions containing PcTX1 (International Peptide or Alomone Labs) were supplemented with bovine

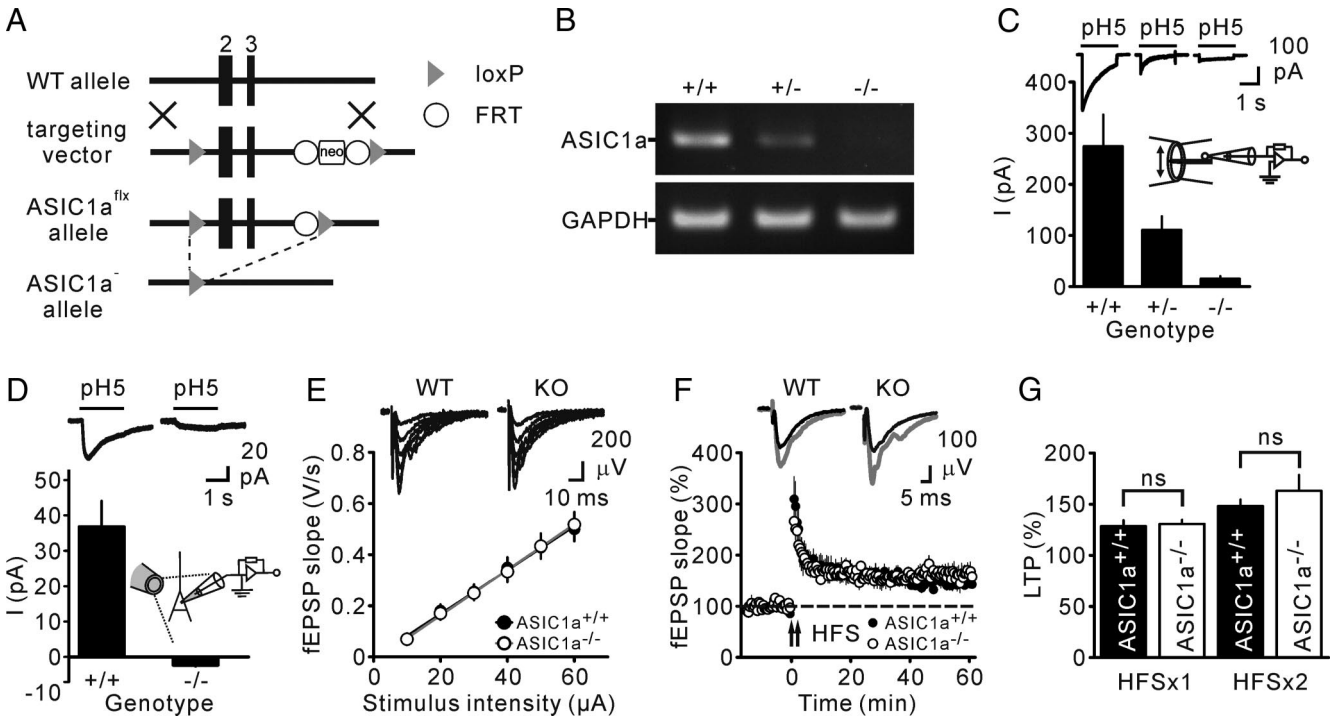

Figure 2. Genetic ablation of ASIC1a did not impair LTP at SC-CA1 synapses. ***A***, A schematic diagram describing the gene targeting strategy and deletion of exons 2 and 3 of *ASIC1a* gene using the Cre/loxP recombination system. ***B***, RT-PCR with whole-brain mRNA from a WT (+/+) littermate and ASIC1a heterozygous (+/−) and homozygous (−/−) KO mice. GAPDH was used as the control. ***C***, Example traces of ASIC-like currents (top) recorded from nucleated patches isolated from interneurons in stratum oriens alveus of WT (+/+; $n = 8$, 4 animals), heterozygous (+/−; $n = 8$, 4 animals), and homozygous (−/−; $n = 8$, 4 animals) mice for ASIC1a deletion and the summary (bottom). Schematic of fast application of proton (pH = 5) on a nucleated patch is shown. ***D***, Example traces of ASIC-like currents (top) recorded from CA1 pyramidal neurons of WT (+/+; $n = 5$, 2 animals) and homozygous (−/−, $n = 6$, 2 animals) mice for ASIC1a deletion and the summary (bottom). Schematic of puff application of proton (pH = 5) on a CA1 pyramidal neuron in the slice is shown. ***E***, SC-CA1 input/output curves of slices from control (WT, *ASIC1a*$^{+/+}$) littermates (filled circles; $n = 6$, 4 animals) and ASIC1a-null (*ASIC1a*$^{-/-}$) mice (open circles; $n = 4$, 2 animals). ***F***, HFS (two trains)-induced LTP was not impaired in slices from *ASIC1a*$^{-/-}$ mice ($n = 5$, 4 animals) compared to that from WT littermates ($n = 5$, 4 animals). ***G***, Summary of LTP induced by different LTP-induction protocols in WT littermates (HFS × 1, $n = 5$, 4 animals; HFS × 2, $n = 5$, 4 animals) and ASIC1a-null mice (HFS × 1, $n = 5$, 4 animals; HFS × 2, $n = 5$, 4 animals).

serum albumin (BSA, 0.05%) to avoid absorption by the tubing. Control experiments were also supplemented with BSA. All other chemicals were from Sigma except where noted.

RT-PCR. Total RNAs were extracted from the whole brain of mice using RNeasy Mini Kit (Qiagen). cDNAs were then synthesized from RNA by random hexamer and SuperScript III First-Strand Synthesis SuperMix (Invitrogen). The primers used for PCR amplification were: ASIC1a, 5′-CACATGCCAGGGGATGCCCC-3′ (forward) and 5′-AGCC GGTGCTTAATGACCTC-3′ (reverse); GAPDH, 5′-GCACAGTCAAGG CCGAGAAT-3′ (forward) and 5′-GCCTTCTCCATGGTGGTGAA-3′ (reverse).

Water maze learning. For the water maze that took place in a circular tank (diameter, 1.2 m) filled with water (20–22°C), a transparent circular platform (diameter 12 cm) was submerged 1 cm below the water's surface in the center of the target quadrant. Behavioral experiments with 2- to 4-month-old ASIC1a-null mice and wild-type (WT) littermates of either sex were conducted blindly. During the 5 d of hidden platform training, two sessions (morning/afternoon) per day and three training trials per session were given. Mice were released from one of the five starting points around the perimeter of the pool (excluding the targeting quadrant) across days. For all trials, mice were allowed to search the platform for 60 s. Animals that did not reach the platform after 60 s were gently guided toward it. Once the mouse reached the platform, the time was recorded as escape latency. Probe test was conducted on day 6. The platform was removed from the tank and the mice were released from a novel start position at the opposite quadrant and allowed to swim in the maze for 60 s. The swimming paths and times of the mice were recorded by a video camera and analyzed by EthoVision video tracking system (Noldus Information Technology).

Data analysis and statistics. Data were analyzed using Clampfit 10.2 (Molecular Devices) and GraphPad Prism 5.0. Values indicate mean ± SEM. Error bars in figures also represent SEM. Statistical significance was tested by the Mann–Whitney rank-sum test at the significance level (p) indicated, using GraphPad Prism 5.0.

Results

Normal LTP is generated after pharmacological blockade of ASICs

In this study, we re-examined the role of ASICs in long-term synaptic plasticity in the rodent hippocampus. It has been found that homomeric ASC1a and heteromeric ASIC1a/2a and ASIC1a/2b channels are major components underlying ASIC-like currents in hippocampal neurons (Baron et al., 2002; Askwith et al., 2004; Weng et al., 2010; Sherwood et al., 2011). A tarantula peptide PcTX1 is the best-known selective inhibitor of ASIC1a (Baron et al., 2002; Chen et al., 2005; Mazzuca et al., 2007) and ASIC1a/2b channels (Sherwood et al., 2011). We first tested the efficacy of PcTX1 on ASIC channels in rat acute hippocampal slices (Fig. 1*A*). H^+-activated currents were induced by focal puffs of pH 6 acidic solution to the somata of recorded cells in the presence of the synaptic blockers kynurenic acid (2 mM) and gabazine (1 μM). Consistent with our previous study (Lin et al., 2010), ASIC-like currents were clearly reduced following bath application of PcTX1. The inhibition of ASIC-like currents was concentration dependent.

We next investigated whether PcTX1 can depress LTP in the rat hippocampal slices. Field potential recordings were made in the CA1 area of the rat hippocampus to assess the effect of PcTX1 on LTP. Here, recordings were performed in the continuous

presence of PcTX1 (30 nM). With four trains of high-frequency stimulation (HFS × 4, 100 Hz stimuli/train; train interval, 20 s), PcTX1 had no detectable effect on the development and maintenance of LTP as compared to the interleaved control slices. The magnitudes of post-tetanic facilitation and LTP in the presence of PcTX1 did not significantly differ from those of control experiments (Fig. 1*B*; control, 151.1 ± 6.6%, $n = 7$; PcTX1, 149.7 ± 16.2%, $n = 6$; $p = 0.95$). When a weak (HFS × 1) induction protocol was used, the magnitude of LTP in the presence of PcTX1 was also similar to that of interleaved control slices (Fig. 1*C*; control, 122.7 ± 7.3%, $n = 5$; PcTX1, 115.5 ± 4.3%, $n = 6$; $p = 0.66$).

Normal LTP is generated in ASIC1a-null mice

To independently test the role of ASIC1a, we used the gene KO mice with deletion of the subunit for ASIC1a (Fig. 2*A*). To achieve this, *ASIC1a*$^{flx/flx}$ mutants in which the second and third exons of the gene *Accn2* flanked by *loxP* sites were crossed with the Nestin–Cre transgenic mice that expressed Cre recombinase under the control of a rat Nestin promoter and the nervous system-specific enhancer (Tronche et al., 1999). This caused recombination between the *loxP* sites and loss of the intervening genomic sequence in their offspring. The deleted genomic region encodes cytoplasmic N terminus, the first transmembrane domain, and a proportion of the extracellular domain. Indeed, ASIC1a transcripts (Fig. 2*B*) and ASIC-like currents (Fig. 2*C*,*D*) were not detectable in the brain of ASIC1a-null (*ASIC1a*$^{flx/flx,Cre/+}$) mutants. Similar to the previous observation (Wemmie et al., 2002), we found that the basal synaptic input/output relationship at Schaffer collateral (SC)-CA1 synapses was not altered in *ASIC1a*$^{-/-}$ mouse slices when compared to interleaved control slices (Fig. 2*E*). In line with our pharmacological experiments, we found that LTP was robustly induced by either one or two HFS protocols and lasted for at least 60 min in *ASIC1a*$^{-/-}$ mouse slices (Fig. 2*F*). The magnitude of LTP induced by the two HFS (HFS × 2) protocols from *ASIC1a*$^{-/-}$ mice was 163.0 ± 13.9% ($n = 5$), comparable to that of 148.3 ± 5.5% ($n = 5$) from control littermates ($p = 0.69$). Also, LTP induced by a weak (HFS × 1) induction protocol was similar in *ASIC1a*$^{+/+}$ and *ASIC1a*$^{-/-}$ mice (Fig. 2*G*, control, 128.5 ± 5.1%, $n = 5$; *ASIC1a*$^{-/-}$, 130.7 ± 3.6%, $n = 5$; $p = 0.84$).

ASIC1a-null mice form spatial memory as well as their WT littermates

In our electrophysiology experiments, we found no evidence for a role of ASIC1a in LTP at SC-CA1 synapses in the hippocampus, casting doubt on the relevance of ASIC1a in spatial learning shown in a previous report (Wemmie et al., 2002). To evaluate the performance of *ASIC1a*$^{-/-}$ mice in hippocampus-dependent spatial learning, we used the Morris water maze paradigm, a classic task for assessing spatial memory in rodents in which the animal must use cues in the environment outside the maze to navigate from start locations around the perimeter of an open swimming arena to locate a submerged escape platform (Morris et al., 1982). Control and mutant mice were subjected to water-maze learning. Results revealed that *ASIC1a*$^{-/-}$ mice had normal acquisition performance in the hidden platform test (Fig. 3*A*). By analyzing their probe trial performance on the next day after the hidden platform test (Fig. 3*B*), we found that there was not a statistically significant difference between *ASIC1a*$^{+/+}$ and *ASIC1a*$^{-/-}$ mice in percentage of time spent in the target (T) zone (*ASIC1a*$^{+/+}$ mice, 49.9 ± 4.9%, $n = 14$ vs *ASIC1a*$^{-/-}$ mice, 55.5 ± 8.6%, $n = 6$; $p > 0.05$). Furthermore, *ASIC1a*$^{-/-}$ mice stayed in the T zone significantly longer than other zones (percent time in the T zone, 55.5 ± 8.6% vs the average time in other zones, 14.8 ± 2.9%, $n = 6$; $p < 0.001$), very similar to the *ASIC1a*$^{+/+}$ group (percent time in the T zone, 49.9 ± 4.9% vs the average time in other zones, 16.7 ± 1.6%, $n = 14$; $p < 0.005$). There was no significant difference in swimming speed between these two groups of mice. Overall, *ASIC1a*$^{-/-}$ mice performed as well as WT littermates in spatial learning and memory.

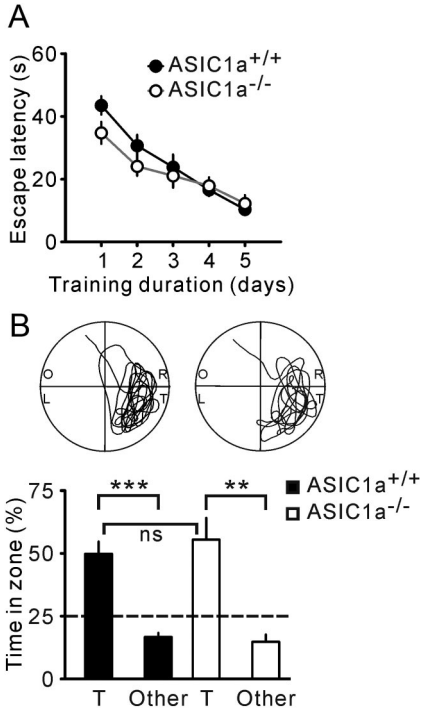

Figure 3. ASIC1a-null mice performed the spatial learning task as well as WT mice. ***A***, Learning curves during spatial training in the hidden platform of the Morris water maze. The latency for each mouse to reach the hidden platform was recorded (*ASIC1a*$^{+/+}$, $n = 14$; *ASIC1a*$^{-/-}$, $n = 6$). ***B***, Top, representative swim traces. T, Target zone; R, right; O, opposite; L, left of target. Bottom, Percent time spent in T zone and other zones during the probe trials (*ASIC1a*$^{+/+}$, $n = 14$; *ASIC1a*$^{-/-}$, $n = 6$). $^{**}p < 0.005$; $^{***}p < 0.001$.

Discussion

We have presented results showing that normal LTP can be generated in the CA1 area of the rat hippocampus in the presence of selective blocker of ASIC1a and ASIC1a/2b channels, indicating no evidence for ASIC-mediated "depolarizing Na^+/Ca^{2+} currents" in facilitating LTP induction if ASIC-mediated postsynaptic currents exist during transmission. We also performed a more stringent test to assess the role for ASIC1a in LTP with ASIC1a-null mice. Contradicting the previous work, we found that LTP was readily induced in mice lacking ASIC1a subunit protein in the brain. Furthermore, we found that *ASIC1a*$^{-/-}$ mice performed a spatial learning and memory task (i.e., Morris water maze) as well as control littermates.

A main conclusion made by Wemmie et al. (2002) is that ASIC1 (ASIC1a)-KO mice had defective spatial memory. To support this claim, they needed to report a statistically significant difference of probe tests between WT and KO mice (Nieuwenhuis et al., 2011). In fact, there was not a statistically significant difference between WT and KO mice in percentage of time spent in the T zone in their study, indicating that ASIC1a-null mice perform spatial memory as well as WT mice. However, when they made separate analyses in each mice group, they noted that WT mice spent a significantly greater amount of time in T quadrant

than in any other quadrant, whereas KO mice did not. Although superficially compelling, the statistical reasoning is erroneous because the difference between significant and not significant need not itself be statistically significant (for a detailed discussion, see Nieuwenhuis et al., 2011). But, does ASIC1a play a role in synaptic function, learning, and memory? Our recent study (P.-Y. Wu, C.-C. Chen, and C.-C. Lien, unpublished observations) showed that synaptic ASIC1a has a potential role in modulating glutamate release and that *ASIC1a*$^{-/-}$ mice do display abnormalities in specific behavioral tasks such as contextual and cued fear conditioning, as reported previously (Wemmie et al., 2003). Therefore, elucidation of the neural mechanisms by which deletion of ASIC1a leads to abnormalities in learning and memory remains a major challenge.

What are the reasons for the discrepancies in our findings and those of Wemmie et al. (2002)? One difference between our study and the previous one is the strategy of deleting *ASIC1a* gene. Wemmie et al. (2002) used the conventional KO strategy to delete exon 2 of the gene *ASIC1* (*Accn2*), which resulted in deletion of the ASIC1a subunit protein. In our case, *ASIC1a*$^{flx/flx}$ mutants in which the exons 2 and 3 of the gene *ASIC1* flanked by *loxP* sites were crossed with the Nestin–Cre transgenic mice that expressed Cre recombinase under the control of a rat Nestin promoter and the nervous system-specific enhancer (Tronche et al., 1999). This caused recombination between the *loxP* sites and loss of the intervening genomic sequence in the central nervous system beginning around embryonic day (E) 10.5. Since ASIC1 mRNA is already abundant by E11 in the mouse brain (García-Añoveros et al., 1997), it is therefore conceivable that deletion of ASIC1a at the very beginning of embryonic stage in Wemmie et al. (2002) might result in a different phenotype. Except for a different strain of ASIC1a-null mice used in our study, the animal's age, the composition of the extracellular solution, the frequency of stimulation during recording of baseline synaptic responses, and the induction protocols were the same or very similar. However, other variables that can affect LTP thresholds, such as the rearing conditions of the animals (Xu et al., 1997; Philpot et al., 2003; Sawtell et al., 2003), may contribute to the discrepancies between our results and those published previously.

In conclusion, we demonstrated that normal LTP is generated after inactivation of ASICs by either pharmacology or genetic deletion approaches. Our results strongly support that activation of ASICs is not essential for induction or maintenance of LTP. This is also consistent with the observation that no postsynaptic ASIC current was detected during neurotransmission (Krishtal, 2003; Wemmie et al., 2006; our observation). Finally, we showed that mice lacking ASIC1a can form spatial memory as well as WT mice. Therefore, we propose that the functional relevance of ASIC1a in synaptic function, learning, and memory should be reassessed.

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