Brief Communications

Dysmyelination of Auditory Afferent Axons Increases the Jitter of Action Potential Timing during High-Frequency Firing

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Auditory neuropathies are linked to loss of temporal acuity of sound-evoked signals, which may be related to myelin loss. However, it is not known how myelin loss affects the waveform and temporal precision of action potentials (APs) in auditory CNS nerve terminals. Here we investigated the excitability of the calyx of Held nerve terminal in dysmyelinated auditory brainstems using the Long–Evans Shaker (*LES*) rat, a spontaneous mutant where compact myelin wrapping does not occur due to a genetic deletion of myelin basic protein. We found at relatively mature postnatal ages (15–17 d after birth) *LES* rat calyces showed prolonged spike latencies, indicative of a threefold reduction in the AP propagation velocity. Furthermore, *LES* rat afferent fiber-evoked APs showed a pronounced loss of temporal precision, even at low stimulation frequencies (10 Hz). While normal calyces were able to fire APs without failures at impressive rates of up to 1 kHz, *LES* calyces were unable to do so. Direct recordings of the presynaptic calyx terminal AP waveform revealed that myelin loss does not affect the AP spike upstroke and downstroke kinetics, but dysmyelination reduces the after-depolarization and enhances the fast after-hyperpolarization peak following the AP spike in the *LES* rat. Together these findings show that proper myelination is essential not only for fast AP propagation, but also for precise presynaptic AP firing that minimizes both spike jitter and failures, two characteristics critically important for the accurate processing of sound signals in the auditory brainstem.

Introduction

Axon diameter, degree of myelination, and the distance between nodes of Ranvier are all important parameters that determine action potential (AP) velocity (Seidl et al., 2010). Myelin reduces the effective membrane capacitance of axons, and thereby serves to speed up AP propagation (Barrett and Barrett, 1982). Accordingly, during postnatal development an increase in compact myelin is paralleled by a 10-fold increase in AP conduction velocity at rat sciatic nerves (Vabnick and Shrager, 1998).

The calyx of Held synapse is part of the ascending auditory pathway that uses submillisecond differences in the timing of binaural signals to compute sound source localization (Carr et al., 2001). At this auditory brainstem synapse previous reports have shown that AP waveform and timing following axonal stimulation changes during early postnatal development (Taschenberger and von Gersdorff, 2000; Leão et al., 2005), perhaps due in part to increased myelination. However, the role of axonal myelination on AP waveform and presynaptic excitability has not been directly tested at CNS bouton-type nerve terminals due to their small size.

Here, we studied the effect of dysmyelination on AP propagation speed, fidelity of timing, and reliability of spiking during low- and high-frequency firing at the large calyx of Held terminal using the Long–Evans Shaker (*LES*) rat. This spontaneous mutant has a severe dysmyelinating phenotype and completely lacks compact myelin in the adult CNS, due to a retroviral genetic lesion that specifically disrupts expression of myelin basic protein (MBP; Kwiecien et al., 1998; O'Connor et al., 1999). Behaviorally, the homozygous *LES* rat has severe shivering, locomotor deficits, and seizures, beginning at ~2 weeks after birth, although the animals are not deaf and can survive for up to 9 months with appropriate care (Smith et al., 2013). We characterized the deficits in AP propagation and reliability in the homozygous mutant and then compared these results to AP firing in normal heterozygous littermates, which showed no behavioral or morphological phenotype and were indistinguishable from wild type. Our findings help to explain how myelin loss can lead to hearing disabilities due to propagation delays and increased timing jitter in the AP transmission along the ascending mammalian auditory pathways (Oertel, 2005; Zeng et al., 2005).

Materials and Methods

Animals. LES rats (obtained from McMaster University, Canada) of either sex were used in accordance with approved Oregon Health and

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Author contributions: J.H.K., R.R., and H.v.G. designed research; J.H.K. and R.R. performed research; J.H.K., R.R., and H.v.G. analyzed data; J.H.K., R.R., and H.v.G. wrote the paper.

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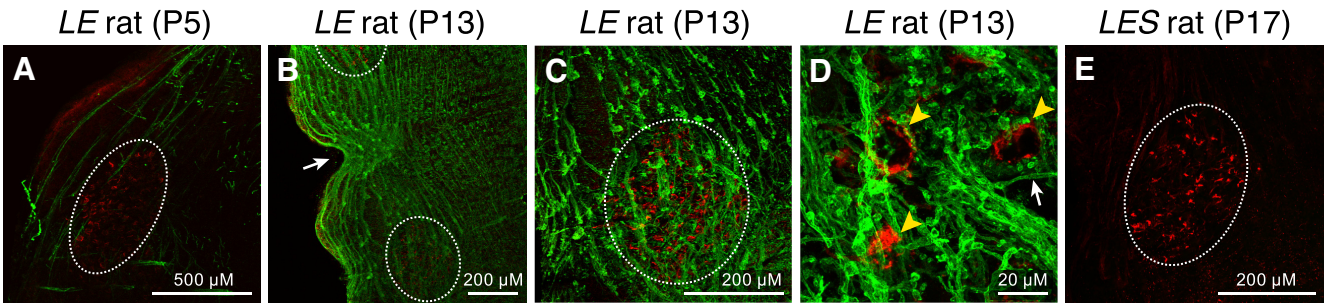

Figure 1. Expression of MBP in the rodent auditory brainstem increases with age. Fixed slices of auditory brainstem containing the ventral stria and MNTB were stained for myelin (MBP; green) and for synaptic vesicles (VGluT1; red). ***A***, In normal young rats (*LE* rat; P5), sparse myelin is present in axonal projections. ***B***, Soon after the onset of hearing (P13), myelin is highly expressed in MNTB axons, and terminates close to the calyx of Held presynaptic terminal. The arrow indicates the midline, where the bipolar stimulus electrode was placed. The areas containing the MNTB are indicated by dotted lines. ***C***, Enlarged image of ***B***, showing staining of presynaptic glutamatergic terminals and myelinated axons in the MNTB. ***D***, Enlarged image of ***C***, showing staining of presynaptic calyx-like terminals (yellow arrowheads) and myelinated axons in the MNTB. The white arrow shows a single isolated myelinated axon. ***E***, A P17 mutant *LES* rat completely lacks staining for MBP, but synaptic vesicle staining (VGluT1; red) in the MNTB appears to be normal.

Science University and University of Texas Health Science Center at San Antonio Institutional Animal Care and Use Committee protocols. Animals were maintained as heterozygotes, and crossed to generate pups homozygous for the MBP mutation. *LES* could be easily identified by gross movement disorders at 2 weeks following birth (Delaney et al., 1995). Heterozygous or wild-type littermates (normal *LE*) showed no abnormalities in behavior, and were used as controls. The breeding of heterozygous pups for obtaining homozygous (*LES* rat) pups was difficult due to the long breeding interval (~3 months) and the extended care that the mutant rats required to stay healthy.

Slice preparation. Transverse brainstem slices (200 μm thick) were prepared from *LE* and *LES* rat pups of postnatal day 15–18 (P15–P18). After rapid decapitation, the brainstem was removed from the skull and immersed in ice-cold artificial CSF (aCSF) for slicing containing the following (in mM): 125 NaCl, 2.5 KCl, 3 $MgCl_2$, 0.1 $CaCl_2$, 25 glucose, 25 $NaHCO_3$, 1.25 NaH_2PO_4, 0.4 ascorbic acid, 3 myo-inositol, and 2 Na-pyruvate, pH 7.3–7.4, when bubbled with carbogen (95% O_2, 5% CO_2; osmolality of 310–320 mOsm). After cutting the slices were transferred to an incubation chamber containing normal aCSF bubbled with carbogen and maintained at 35°C for 30 min, and thereafter at room temperature. Normal aCSF was the same as slicing aCSF, but with 1 mM $MgCl_2$ and 2 mM $CaCl_2$.

Electrophysiology. Whole-cell patch-clamp recordings were performed in normal aCSF at room temperature (22−24°C) or 35°C (see Fig. 4*C*). Pipette solution contained the following (in mM): 130 K-gluconate, 20 KCl, 5 Na2-phosphocreatine, 10 HEPES, 4 Mg-ATP, 5 mM EGTA, and 0.3 GTP, pH adjusted to 7.3 with KOH. Presynaptic APs were recorded using the fast current-clamp mode of the EPC-10 amplifier (HEKA). Current-clamp recordings were continued only if initial uncompensated series resistance R_s <20 MΩ. Membrane potentials were not corrected for a calculated liquid junction potential of 11 mV. Presynaptic APs were elicited with a bipolar electrode and an Iso-Flex (A.M.P.I.) stimulator delivered 100 μs pulses <15 V. Data were acquired at 20–100 kHz and filtered on-line at 2.9 kHz. Differences were considered statistically significant when $p < 0.05$ by Student's t test.

Immunohistochemistry. Brainstem slices (150–200 μm) were fixed with 4% (w/v) paraformaldehyde in PBS for 60 min. Free-floating sections were permeabilized 30 min with 0.5% Triton X-100. For staining, slices were blocked in 0.3% goat serum in PBS and incubated overnight at 4°C with mouse monoclonal anti-myelin basic protein (1:4000; Sternberger Monoclonals), or monoclonal guinea pig anti-vesicular glutamate transporter 1 (VGluT1) antibody (1:1000, Millipore Bioscience Research Reagents). Staining was reported by incubation with appropriate Alexa dye-conjugated secondary antibodies for 2 h at room temperature. Slices were mounted onto SuperFrost slides in photobleaching-protective medium. Stained slices were viewed with laser lines at 488 and 633 nm using a 60× oil-immersion objective on a confocal laser-scanning microscope (Olympus FluoView 300).

Results

Myelin loss significantly reduced AP firing precision

In normal *LE* rat brain slices, we detected the presence of myelin in the ventral striatum of the auditory brainstem, projecting to the medial nucleus of the trapezoid body (MNTB), using an antibody for MBP (Fig. 1, green). Axons innervating the immature MNTB (P5–P6) showed sparse staining for MBP ($n = 7$; Fig. 1*A*). However, myelin was highly expressed in MNTB axons soon after the onset of hearing at P13 ($n = 7$; Fig. 1*B*, green). Myelin terminated near the calyces of Held (stained red with antibody for VGluT1; Fig. 1*C*,*D*), but was excluded from the 20–50 μm heminode region of the preterminal axon (Leão et al., 2005). Brainstem slices from *LES* rats showed similar expression of VGluT1 as the control, but no staining for MBP (Fig. 1*E*). This suggests that the calyx synapse formation and morphology in *LES* rats is not grossly disturbed by the MBP mutation.

To test the effect of myelin loss on the timing of presynaptic APs, we examined presynaptic spikes using noninvasive cell-attached recordings and also in whole-cell patch-clamp recordings of APs from normal rats (*LE*; control) and in dysmyelinated axons from *LES* rats (*LES*). The AP spike recorded in the calyx is initiated at the distal axon near the tip of the bipolar stimulation electrode in the brainstem midline and then propagates to the calyx terminal (Paradiso and Wu, 2009). Both cell-attached and whole-cell recordings from normal calyx terminals at P16 revealed that presynaptic spike timing is very precise and reliable; however, the *LES* rats showed pronounced timing errors of presynaptic APs. In *LES*, we observed increased AP latency and increased temporal jitter at 10 Hz stimulation, even at nearly 3 weeks after birth (Fig. 2). We compared the conduction velocity in presynaptic terminals from normal myelinated axons with dysmyelinated axons by measuring spike latency in noninvasive cell-attached recordings and AP latency in whole-cell recordings, as the time delay from the stimulation artifact to the cell-attached spike or whole-cell AP peak, respectively. We placed the bipolar afferent fiber stimulator on the midline of auditory brainstem slices (Fig. 1*B*, arrow), which is ~300–400 mm away from the MNTB. Remarkably, the mutant *LES* exhibited a nearly twofold longer spike latency (1.27 ± 0.15 ms vs 0.69 ± 0.07 ms, $n = 7$ and 8, respectively; Fig. 2*A*) between stimulus artifact and spike peaks in cell-attached recordings. In the same patch recordings, after achieving the whole-cell configuration, AP latency was 1.49 ± 0.25 ms versus 0.52 ± 0.06 ms (Fig. 2*B*,*C*), a nearly threefold

change in latency. Given that the distance between the bipolar stimulating electrode and the locations of the patch recordings was ~400–800 μm (Fig. 1*B*), we estimate the AP conduction velocity in the axon was ~0.8–1.5 m·s^{-1} in *LE* rats at room temperature, and threefold slower in *LES* rats. Additionally, the temporal precision of the APs was degraded in *LES* rats (jitter range: 255 ± 41 μs in P16–P18 *LES* rats vs 62 ± 8 μs in normal *LE* rats, $p < 0.001$, $n = 5$; Fig. 2*C*). This increased jitter may be related to the slow AP speed in *LES* rats, which prolongs the delay time between spike initiation in the distal axon and spike arrival in the nerve terminal. Note that for long axons even small variations in AP speed will produce large differences in spike arrival times (Wang et al., 2008).

Axonal myelination affects the waveform of the presynaptic APs

We examined presynaptic AP waveforms in myelinated or dysmyelinated axon terminals from *LE* and *LES* rats. There was no significant difference in AP amplitude (118 ± 6.0 and 109 ± 6.0 mV in control and the *LES*, respectively, $n = 5$) or half-width (214 ± 34.7 and 183 ± 64.3 ms, respectively; cf. Fig. 2) at room temperature. Moreover, the average resting membrane potentials of *LE* and *LES* calyces are not significantly different (−79.8 ± 0.6 mV and −78.5 ± 0.8 mV, $n = 6$, $p = 0.2$). A normal *LE* rat at P15–P18 shows a large after-depolarization (ADP) with amplitude 11.4 ± 3.0 mV (from the peak of fast after-hyperpolarization (fAHP) to the peak of ADP) and decay time constant of 8.2 ± 1.8 ms ($n = 5$). These results are comparable to those in normal Sprague Dawley rats at P16 (13.8 ± 0.6 mV, $n = 4$; Kim et al., 2010). However, P16–P18 *LES* rats displayed a smaller ADP (7.8 ± 1.3 mV from the peak of fAHP to the peak of ADP) with a fast decay (9.2 ± 2.1 ms, $n = 5$; Fig. 3*A*). Moreover, in *LES* rats the peak of the fAHP was more hyperpolarized (−82.3 ± 0.8 mV vs −77.8 ± 1.5 mV in control, $n = 5$, $p < 0.05$; Fig. 3*B*). Thus, the peak potential of the ADP measured from the resting membrane potential was significantly reduced to 3.9 ± 0.9 mV in *LES* rats from the normal *LE* value of 11.5 ± 2.2 mV ($n = 6$, $p = 0.014$; Fig. 3*C*). Because a larger peak potential of the ADP facilitates the firing of subsequent spikes during a stimulus train (Fig. 4*B*, bottom superimposed traces; Kim et al., 2010), we suggest that a more hyperpolarized fAHP peak and smaller ADP in *LES* promotes a reduction in the reliability of repetitive firing at dysmyelinated MNTB axons.

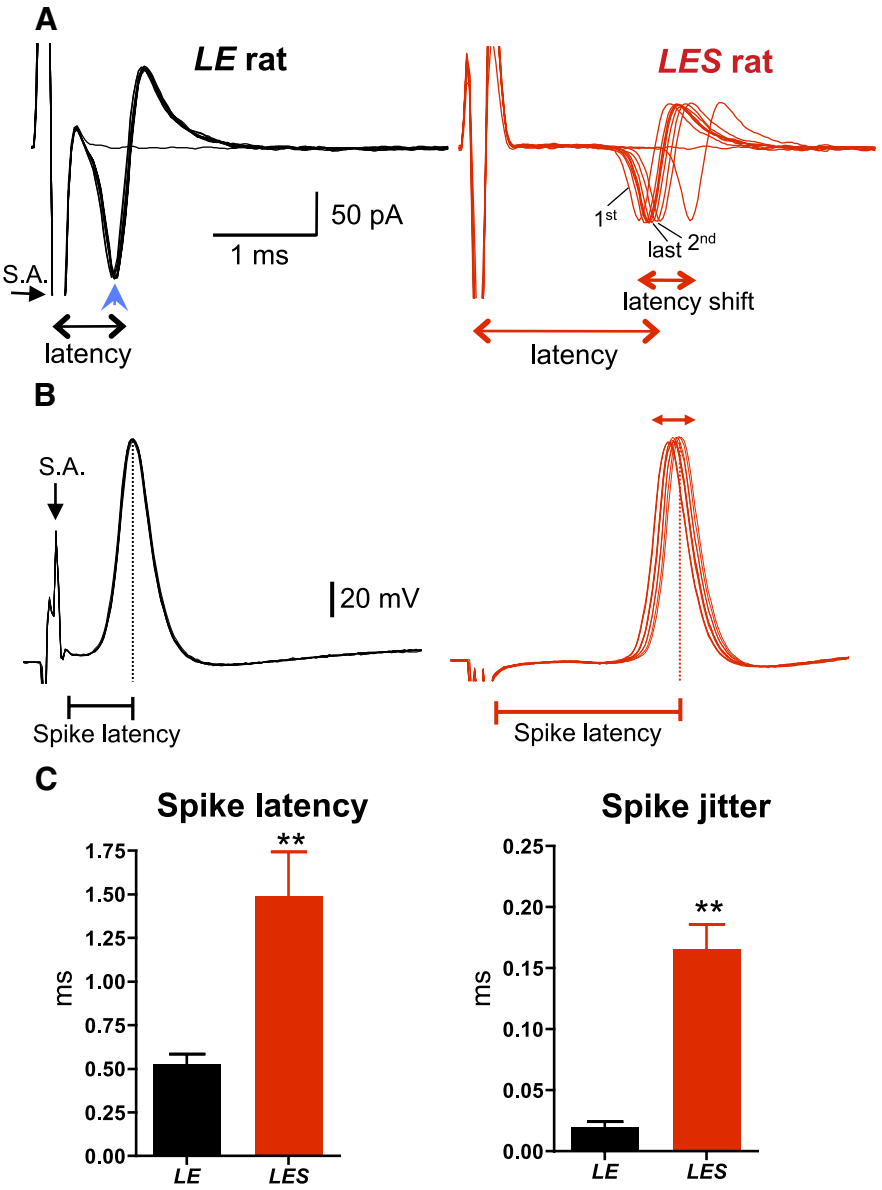

Figure 2. *LES* rats show increased presynaptic spike latency and a lack of temporal precision during 10 Hz repetitive firing. ***A***, Afferent fiber stimulation at 10 Hz (10 stimulus pulses) results in presynaptic extracellular spikes when recorded in the cell-attached mode at a P17 calyx terminal: normal *LE* (black trace) and the *LES* mutant rat (red trace). Note the large latency shift (and temporal jitter) in the *LES* rat spikes (the labels first, second, and last indicate the order of responses to 10 Hz afferent fiber stimulation). One subthreshold trace is shown. ***B***, Presynaptic action potentials from the same calyx recordings as shown in ***A*** in whole-cell current-clamp mode. Note the lack of precision (or jitter) in the timing of the spikes for *LES* mutants. ***C***, Summary of the spike delay and jitter in *LE* and *LES* rats (**$p < 0.001$). S.A., stimulus artifact.

Axon myelination is critical for repetitive firing with high precision and fidelity

We next examined the reliability of AP firing in dysmyelinated axons at high stimulation frequencies. Both normal *LE* and *LES* calyx terminals at P16–P17 can spike without failure at 100 Hz (Fig. 4*A*). However, *LES* calyx terminals at P16–P17 showed intermittent AP failures during a stimulus train of 300 Hz, while a normal calyx could fire spikes without failure at 300 Hz (Fig. 4*B*). In six of seven recordings from *LES* calyces at P16–P18, APs often failed to fire during 300 Hz AP trains (50 pulses). AP failures were intermittent, indicating that an AP triggering or propagation failure occurs along dysmyelinated axons. Increasing the stimulation intensity could not completely recover the failure of APs at dysmyelinated axons at 300 Hz stimulation (data not shown). In addition, raising the temperature of the bath solution from 24 to 37°C allowed the normal P16–P17 *LE* calyx terminals to fire APs without failures at 1 kHz in normal calyces, but not at *LES* calyces (Fig. 4*C*). Our results indicate that loss of compact myelin reduces the reliability of spike firing at higher stimulation frequen-

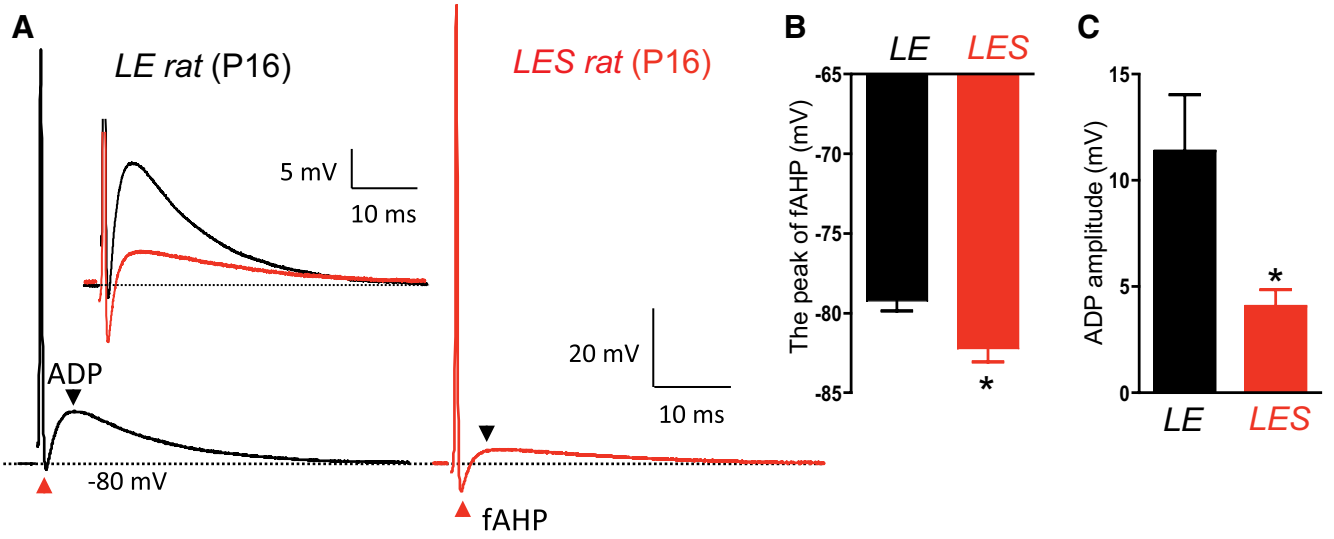

Figure 3. *LES* calyx terminals have a smaller ADP and an enhanced fAHP peak. Afferent fiber stimulation produced an action potential with an ADP in a P16 normal *LE* calyx recording (black; ***A***) and an ADP with a reduced peak value in a calyx from the *LES* (right, red trace). Both calyces displayed an ADP (black arrowhead) and fAHP (red arrowhead). Inset, Same traces on an expanded voltage scale. ***B***, Peak reversal voltage of fAHP was significantly larger in calyces from *LES* than *LE*, recorded from P15–P18 rats. ***C***, Summary of the ADP amplitude, measured from resting potential to the peak of ADP in normal *LE* and mutant *LES* calyces in P15–P18 rats.

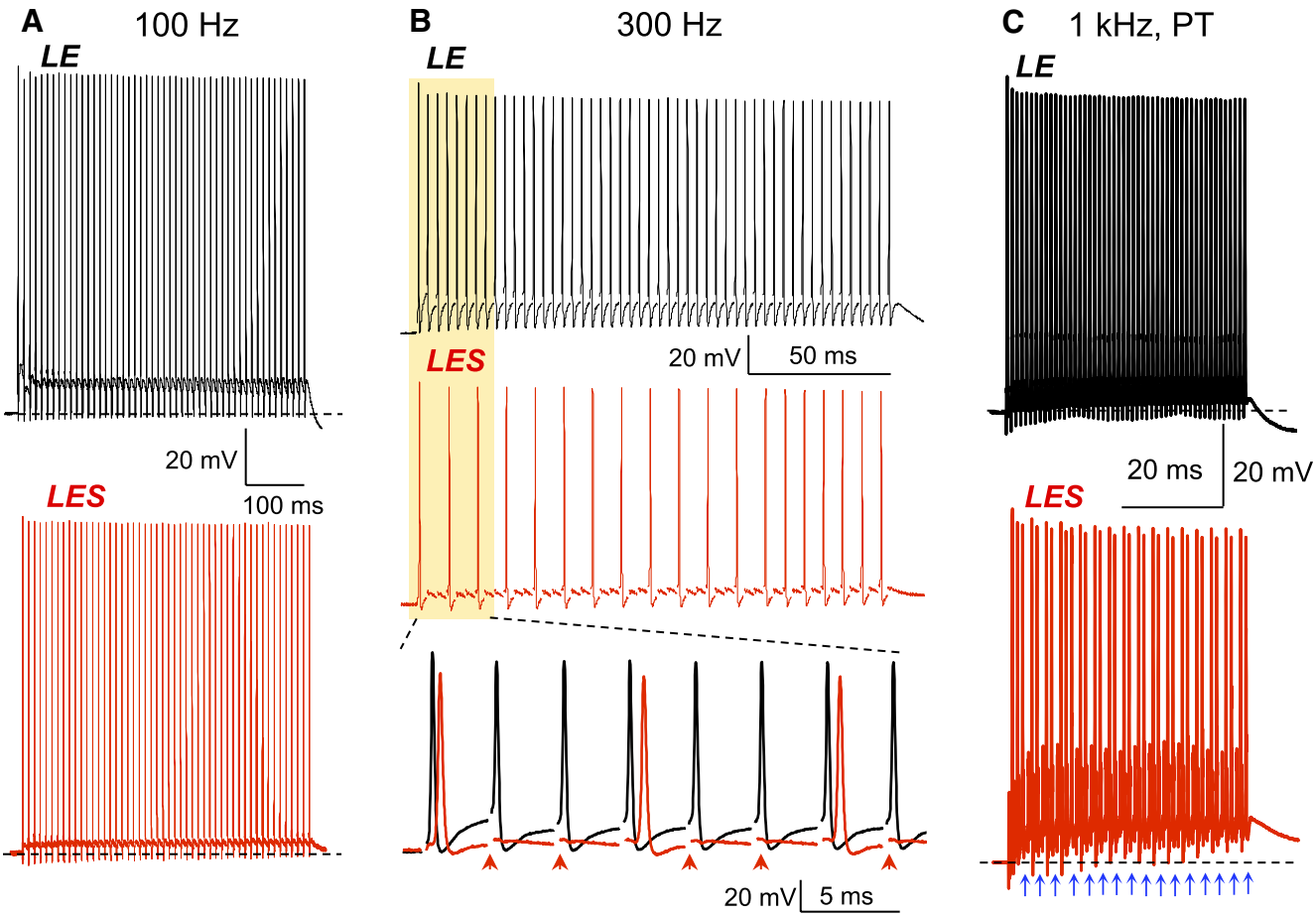

Figure 4. *LES* calyx terminals cannot follow APs at higher frequencies. AP trains were triggered at 100 Hz (***A***), 300 Hz (***B***), and 1 kHz (***C***) at room temperature (24°C, ***A*** and ***B***) and at physiological temperature (PT; 37°C, ***C***). The calyx of Held of both *LE* and *LES* rats can follow 100 Hz stimulation, but at higher stimulation frequencies (300 Hz and 1 kHz) presynaptic APs of the *LES* calyx terminals experience intermittent failures, whereas normal *LE* calyx terminals can routinely follow 300 Hz (at room temperature) and even 1 kHz at 37°C without AP failures. Recordings were from P16 *LE* and *LES* rats (black and red traces, respectively). The horizontal dashed line indicates the resting membrane potential of −80 mV. Arrowheads in ***B*** and blue arrows in ***C*** indicate AP failures. *LES* rats showed more AP failures and the timing of the APs showed more "jitter."

cies. Thus, myelin is crucial for the ability of the calyx of Held's axon to follow repetitive firing with high precision and fidelity.

Discussion

Direct presynaptic terminal recordings from the calyx of Held in *LES* rats revealed that myelin loss reduces AP timing fidelity and reliability. We found that central dysmyelination affects not only AP spike velocity, but importantly for the auditory system, also the exact presynaptic spike timing and reliability. The *LES* rat axons that terminate as calyces of Held thus provide an elegant model system for understanding the pathophysiological effects of reduced compact myelin in the CNS.

Myelination renders axons and nerve terminals capable of reliable high-frequency firing with high temporal precision

Previous characterization of *LES* rats showed that there is no condensed myelin in the CNS (Kwiecien et al., 1998; Smith et al., 2013). Accordingly, our immunohistochemistry analysis shows that the *LES* rat MNTB does not stain with MBP antibody (Fig. 1*E*). Myelination is important for the clustering of $Na_v1.6$ channels at nodes of Ranvier during development, and for the rapid, reliable, and efficient propagation of action potentials along axons (Vabnick and Shrager, 1998). Dysmyelination is known to increase the expression of ectopic Na and K channels on axons (Waxman et al., 2004; Sinha et al., 2006). This may greatly decrease their input resistance of the internode membrane, which together with an increase in membrane capacitance will greatly slow the speed of the AP. *LES* axons exhibit improper localization of internodal (Kv1.1, 1.2 channels) and paranodal proteins (e.g., Caspr) in spinal cord axons (Eftekharpour et al., 2005). This may lead to decreased amplitudes and increased spike latency in extracellular field recordings in *LES* rats, although these previous studies did not report an increased jitter in spike timing (Eftekharpour et al., 2005). The *shiverer* mouse, a homolog of the *LES* rat, also has axons with a dispersed distribution of K^+ channels along the internodes (both Kv1.1 and Kv12; Sinha et al., 2006) and retarded Na-channel clustering, which result in immature field potentials and increased AP latencies (Rasband et al., 1999; Bando et al., 2008).

P16–P18 *LES* calyces showed a threefold slower AP propagation velocity than normal calyces, and *LES* calyces had almost a fourfold decrease in presynaptic spike timing precision (i.e., increased jitter) compared with myelinated calyces at 10 Hz stimulation (Fig. 2). We suggest that this increased spike timing variability in the *LES* calyces may be linked to the slower AP conduction speed in the mutant *LES* afferent fibers.

Myelin loss affects the exact AP waveform at nerve terminals

Axons undergo a sequence of excitability changes after the conduction of a nerve impulse, related to after-potentials following an AP spike; the ADP and AHP (Bostock and Rothwell, 1997). In addition to the refractory period, axonal ADP and AHP determine superexcitability or subexcitability of motor axons (Bostock et al., 2005). In the auditory system, the exact timing of spikes is used to encode sound intensity and pitch. Thus, the ADP and AHP at auditory axons may modulate neuronal entrainment by sound. The mature calyx of Held exhibits a fast AHP, and after the AP spike an ADP characterized by a fast upstroke phase and a slower decay phase (Kim et al., 2010). Our results show that the fast AHP and ADP are both affected by myelin loss in the *LES* rats (Fig. 3). Previous studies have shown that active resurgent Na^+ currents or K^+ currents affect the amplitude of the ADP (Dodson et al., 2003; Kim et al., 2010), and passive discharge currents regulate the decay phase of the ADP (Borst et al., 1995). At the calyx of Held, tetraethylammonium (TEA)-sensitive Kv3 channels contribute to shorter AP waveforms and more reliable spiking at high frequencies (Wang et al., 1998; Nakamura and Takahashi, 2007). In particular, the TEA-sensitive Kv3 channel and Na 1.6 channels, which increase in density during development, underlie the presynaptic fAHP and ADP, respectively, in the calyx of Held (Kim et al., 2010). We thus suggest that the number of active Na^+ channels is reduced in *LES* axons because the ADP is reduced in size. In addition, the AP trains showed more failures during high-frequency stimulation (e.g., 300 Hz or 1 kHz; Fig. 4) in the mutant *LES* rats, which may also be caused by reduced Na^+ channel densities. Accordingly, treatment of axons with low doses of tetrodotoxin leads to more AP failures during high-frequency trains (Madeja, 2000).

Hearing disorders and dysmyelination of auditory afferent fibers

Symptoms of multiple sclerosis (MS) can include loss of hearing acuity (Noffsinger et al., 1972). In cases with hearing loss, 85% show sensorineural bilateral high-frequency loss (Peyvandi et al., 2010). This typical symptom of hearing loss in MS is similar to those shown in auditory neuropathy (Starr et al., 2000; Rance, 2005). Recent studies have suggested that auditory neuropathy is closely related to disrupted neuronal synchrony, resulting perhaps from impaired hair cell ribbon synapses, myelin damage, or a reduction in the number of functioning fibers (Oertel, 2005; Rance, 2005). Here, we examined the effect of myelin loss specifically on AP firing at the single axon and nerve terminal level in the mammalian auditory brainstem. Our results suggest that abnormalities in timing of AP firing due to dysmyelination may lead to problems in understanding speech for some auditory neuropathy patients (Zeng et al., 2005).

In conclusion, our results show that myelination reduces spike jitter, promoting the precise encoding of the timing of sound signals in the ascending auditory system. The fast propagation velocities of APs in myelinated axons make them better suited to transmit spike timing information than unmyelinated axons, because fast conduction speeds minimize the conduction delay of spikes over long distances (Wang et al., 2008). The evolution of myelination in vertebrate animals thus provided major advantages: more precise spike timing and greater dynamic range of spike rate encoding to convey sensory and motor information across long distances in the CNS, with minimal use of metabolic energy and with reduced jitter.

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