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TEMPORAL PROCESSING CAPACITY IN AUDITORY-DEPRIVED SUPERIOR PARAOLIVARY NEURONS IS RESCUED BY SEQUENTIAL PLASTICITY DURING EARLY DEVELOPMENT

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Abstract—The leading treatments for severe hearing disabilities work on the principle of conveying electrical pulses to the auditory brainstem that enable perception of speech. It is currently not known how well the brainstem neurons specialized for decoding such coarse sound information develop when deprived of auditory input activity. Here, we used congenitally deaf $\alpha1D^{-/-}$ mice, lacking activity in the auditory nerve, to investigate the superior paraolivary nucleus (SPON) – a prominent mammalian brainstem structure that responds selectively to sound pulses by rebound spiking. Whole-cell patch-clamp recordings from SPON neurons in the $\alpha1D^{-/-}$ and control mice were obtained at equivalent pre- and post-hearing onset ages. The results show that SPON neurons in the $\alpha1D^{-/-}$ display less precise, plateau-like rebound spiking compared to control neurons. However, the rebound spiking mechanism undergoes strong compensation with age in the $\alpha1D^{-/-}$. Voltage-activated Ca^{2+}-currents lower the spike threshold, rescuing the capacity for spike initiation at pre-hearing onset ages. Gradual up-regulation of the inwardly rectifying h-current contributes to depolarize the membrane potential. Reduction of the membrane time constant and less recruitment of Ca^{2+}-currents thereby normalize precise rebound spiking at post-hearing onset ages. We found the soluble form of the neurotrophic factor neuritin to be up-regulated in SPON of deaf mice, which may have promoted neuronal survival and prolonged plasticity of the SPON circuitry. A stereotyped timeline of compensation of rebound spiking in deaf SPON neurons indicates robust intrinsic regulation of the brainstem circuitry encoding sound rhythms. This may be a prerequisite for successful cochlear implants.

Key words: deaf, brainstem, rebound spiking, h-current, neuritin.

INTRODUCTION

Hearing plays a fundamental role for language development (Kuhl, 2010). Even the earliest proto-communication between mother and infant is crucial for the development of adult language skills (Werker and Tees, 1992). Children born with partial or complete deafness consequently fail to develop adequate speech and language skills if left untreated. However, fitting these children with cochlear implants (CIs) early in development will substantially increase their chances of acquiring near-normal language skills (Svirsky et al., 2004). The beneficial effect of electrical stimulation via CIs is strictly age dependent, coinciding with a critical period for cortical organization during development (Kral et al., 2001, 2002). Since prolonged auditory deprivation has adverse impact on higher cortical functions, such as working memory (Pisoni and Geers, 2000), motor coordination (Horn et al., 2006, 2007), and selective attention (Colletti, 2007), it further stresses the importance of providing early auditory experience (Kral and Sharma, 2012). However, the outcomes of an auditory prosthesis for optimal acquisition of speech and language skills vary considerably, even if implanted within the recommended time frame (Colletti et al., 2013; Lammers et al., 2015a). This variability may arise from alterations in sub-cortical processing, as indicated by auditory brain response waveforms in CI-implanted patients (Gordon et al., 2008; Sparreboom et al., 2010; Lammers et al., 2015b,c) and congenitally deaf cats (Tillein et al., 2012). Seemingly intact afferent connectivity in the deaf condition (Russell and Moore, 1995; Heid et al., 1997; Oleskevich and Walmsley, 2002; Oleskevich et al., 2004; Youssoufian et al., 2005) suggests that, if there are deficits in auditory brainstem processing, they may be related to cellular properties. Plenty of cellular atrophic changes (Nordeen et al., 1983; Anniko et al., 1989; Saada, 1996; Redd et al., 2002), and altered intrinsic properties (Oleskevich and Walmsley, 2002; Leão et al., 2004, 2005; Wang and Manis, 2006; Hassfurth et al., 2009; Couchman et al.,

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Abbreviations: aCSF, artificial cerebrospinal fluid; BDNF, brain-derived neurotrophic factor; CI, cochlear implant; EGTA, ethylene glycol-bis(β-aminoethyl ether)-N,N,N′,N′-tetraacetic acid; FSL, first spike latency; HCN, hyperpolarization-activated cyclic nucleotide-gated; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; Ih, h-current; IR, inwardly rectifying; KCC2, potassium chloride co-transporter 2; Kir, inwardly rectifying potassium current; KO, knock-out; LSO, lateral superior olive; MNTB, medial nucleus of the trapezoid body; P, postnatal; PBS, phosphate-buffered saline; RD, rebound depolarization; SOC, superior olivary complex; SPON, superior paraolivary nucleus; TrkB, tyrosine receptor kinase B; WT, wildtype.

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2011; Butler and Lomber, 2013) have been documented following auditory deprivation of the brainstem.

In this study, we investigated neurons of the superior paraolivary nucleus (SPON), a prominent mammalian auditory brainstem structure proposed to encode rhythmic sound features, important for animal vocalizations and human speech (Grothe, 1994; Kuwada and Batra, 1999; Behrend et al., 2002; Dehmel et al., 2002; Kadner and Berrebi, 2008; Felix et al., 2011; Kopp-Scheinpflug et al., 2011; Felix et al., 2013). Despite a consensus on the importance of preserving rhythmical sound information for an optimal outcome of auditory prostheses (Wilson et al., 1991; Rauschecker and Shannon, 2002), the SPON has been overlooked in congenital deafness models. The $\alpha 1D^{-/-}$ mouse has a functional knockout (KO) of Cav1.3 ion channels (Platzer et al., 2000). This HVA L-type calcium channel subunit is essential for neurotransmitter release from cochlear inner hair cells onto the afferent neurons of the auditory nerve (Engel et al., 2002; Brandt et al., 2003). Consequently, these KO mice lack both spontaneous and sound-driven auditory nerve activity (Platzer et al., 2000). To determine whether auditory-deprived SPON neurons have a normal functional output, we compared the development of the rebound spiking mechanism (Felix et al., 2011; Kopp-Scheinpflug et al., 2011) in congenitally deaf $\alpha 1D^{-/-}$ mice and normally hearing mice. Our results demonstrate that, compared to hearing mice, the maturation of the rebound spiking in auditory-deprived SPON neurons follows abnormal but robust rules, preserving the capacity for precise sound rhythm detection. An upregulation of the sensory neurotrophic factor neuritin may have supported this neural compensation.

EXPERIMENTAL PROCEDURES

Slice preparation and solutions

Wildtype CBA/CaJ mice and congenitally deaf mice bread on a C57BL/6 background with a knocked out 1D isoform of the pore-forming α-subunits of the voltage-gated L-type Ca^{2+} channel isoform ($\alpha 1D^{-/-}$; Platzer et al., 2000), were used. A postnatal (P) developmental stage from P5 to P15 was studied. Animals were decapitated under sodium pentobarbital anesthesia in conformity with the rules set by the European Commission Council Directive (86/89/ECC) and approved by the local Swedish Animal Care and Use Committee (Permit N52/13). Following decapitation, the brainstem was collected and placed in low-sodium, high-sucrose artificial cerebrospinal fluid (aCSF) containing (in mM) 85 NaCl, 2.5 KCl, 1.25 NaH_2PO_4, 25 $NaHCO_3$, 75 sucrose, 25 glucose, 0.5 $CaCl_2$, and 4 $MgCl_2$. Coronal brainstem slices containing the SPON were obtained at a thickness of 180–220 μm using a Vibratome (model VT1200; Leica, Wetzlar, Germany) and incubated at 32 °C in normal aCSF containing (in mM) 125 NaCl, 2.5 KCl, 1.25 NaH_2PO4, 26 $NaHCO_3$, 25 glucose, 2 $CaCl_2$, and 1 $MgCl_2$ for 30 min, after which they were allowed to cool to room temperature. aCSF was continuously bubbled with carbogen gas (95% O_2–5% CO_2), setting the pH to 7.4. For current-clamp and voltage-clamp recordings, the internal pipette solution contained (in mM) 130 K-gluconate, 5 KCl, 10 HEPES, 1 EGTA, 2 Na_2-ATP, 2 Mg-ATP, 0.3 Na_3-GTP, and 10 Na_2-phosphocreatinine, adjusted to pH 7.3 with KOH.

Recording procedures

Slices were transferred to a recording chamber perfused (~3 ml min^{-1}) with oxygenated aCSF at room temperature. SPON principal cells were viewed with an upright microscope (Axioscope; Zeiss, Oberkochem, Germany) equipped with a digital CCD camera (Orca 2; Hamamastu, Japan) using a 40x water-immersion objective (Zeiss Achroplan) and infrared-differential interference optics. SPON cells were initially identified visually by their large somata in a defined area medial to the lateral superior olive (LSO) and, subsequently, identified physiologically by their rebound spiking response to hyperpolarization (Felix et al., 2011). Neuron capacitance was estimated from the compensation measurement under voltage-clamp. Whole-cell current- and voltage-clamp recordings were performed with a Multiclamp amplifier (700B; Molecular Devices, Sunnyvale, USA) using borosilicate glass microelectrodes with a final tip resistance of 5–10 MΩ. The bridge balance was applied for current-clamp recordings. During voltage-clamp recordings, the series resistance was compensated by 70–80%. Voltages were not corrected for a liquid junction potential (11.6 mV). Possible differences in cellular properties of SPON neurons inherent to mouse strain background (CBA/CaJ and C57BL/6) have previously been shown to be non-significant (Felix et al., 2011), and thus not considered in this study.

Data acquisition and analysis

Recorded signals were sampled at 20 kHz, filtered with a low-pass four-pole Bessel filter at 10 kHz, and digitized using a Digidata 1422A interface (Molecular Devices). Stimulus generation, data acquisition, and off-line analysis of data were performed using the pClamp software (version 10.2; Molecular Devices) or IgorPro (version 6.12A; WaveMetrics, Lake Oswego, USA). The input resistance was estimated from the voltage deflection induced by a −100 pA hyperpolarizing current step and the membrane time constant was measured after the offset of the current step by fitting a single-exponential function to the voltage trace (Felix et al., 2013). The activation time constants of the inwardly rectifying (IR) currents in SPON neurons were obtained by fitting a double-exponential function to the current traces (Hassfurth et al., 2009). Chirp stimuli were generated in MATLAB (MathWorks Inc., Natick, USA), imported into the amplifier software, and scaled appropriately with a gain function. The tuning of a neuron to chirp stimuli was determined as the mean frequency at which the respective neuron fired spikes at rheobase (i.e., the lowest magnitude of stimulation needed to evoke an action potential). Results are expressed as mean ± the standard error (SE) of the mean in the text and figures. Data did however not meet the criteria for normal distribution according to Shapiro–Wilks analysis, and therefore the level of significance was determined by a non-