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Research paper

Development of response selectivity in the mouse auditory cortex

María Magdalena Carrasco, Michael Trujillo, Khaleel Razak*

Graduate Neuroscience Program and Psychology Department, University of California, 900 University Avenue, Riverside, CA 92521, USA

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ABSTRACT

The mouse auditory system contains neurons selective for tone duration and for a narrow range of frequency modulated (FM) sweep rates. Whether such selectivity is developmentally regulated is not known. The main goal of this study was to follow the development of neuronal responses to tones (frequency and duration tuning) and FM sweeps (direction and rate selectivity) in the core auditory cortex (A1 and AAF) of ketamine/xylazine anesthetized C57bl/6 mice. Three groups were compared: postnatal day (P) 15–20, P21–30 and P31–90. Frequency tuning bandwidth decreased during the first month indicating refinement of the excitatory receptive field. Duration tuning for tones did not change during development in terms of categories of tuning types as well as measures of selectivity such as best duration and half-maximal duration. FM rate and direction selectivity were developmentally regulated. Selectivity for linear up and down FM sweeps (0.06–22 kHz/ms) was tested. The best rate and half-maximal rate of neurons categorized as fast- or band-pass selective shifted toward faster rates during development. The percentage of fast-pass selective neurons also increased during development. These data suggest that cortical neurons' discrimination and detection abilities for relatively faster sweep rates improve during development. Although on average, direction selectivity was weak across development, there was a significant shift toward upward sweep selectivity at slow rates. Thus, the C57bl/6 mouse auditory cortex is not adult-like until at least P30. The changes in response selectivity can be explained based on known developmental changes in intrinsic and synaptic properties of mouse auditory cortical neurons.

1. Introduction

Response properties in the auditory cortex show developmental changes and such changes are influenced by experience (Barkat et al., 2011; de Villers-Sidani et al., 2007; Insanally et al., 2010; Oswald and Reyes, 2008; Razak et al., 2008; Vater et al., 2010). The mouse is a useful model to tease apart activity-dependent and -independent factors in the development of response selectivity (Barkat et al., 2011; Demyanenko et al., 2011; Gianfranceschi et al., 2003; Intskirveli et al., 2011; Ranson et al., 2012; Sugiyama et al., 2008; Torii et al., 2012; Xu et al., 2011). The focus of the present study was to determine the normal developmental time course of spectral, temporal and spectrotemporal selectivity in the mouse auditory cortex. This will provide baseline measures for investigations in transgenic models of diseases with auditory communication implications. We focused on developmental time periods between post-natal (P) days 15–30 and compared the responses with those found in adult (P31–P90) because *in vitro* studies show changes in intrinsic and synaptic properties in the mouse auditory cortex between P15 and P30 (Oswald and Reyes, 2008, 2011).

The first goal of this study was to follow the development of responses to pure tones with a focus on frequency and duration tuning in the core auditory cortex (both primary auditory cortex, A1 and the anterior auditory field, AAF) of the mouse (strain C57bl/6) auditory cortex. Sharp frequency tuning is a defining feature of core auditory cortex and it develops relatively early compared to temporal processing features of the cortex (see Froemke and Jones, 2011 for review). Duration tuning for tones is found in auditory systems across vertebrate taxa and is likely to be important in temporal (Brand et al., 2000; Casseday et al., 1994; Chen, 1998; Fuzessery and Hall, 1999; Perez-Gonzalez et al., 2006; Wang et al., 2006) and spectrotemporal processing (Fuzessery et al., 2006) of behaviorally relevant sounds. Whether duration tuning in the mouse auditory cortex is similar to that found in the mouse inferior colliculus (IC, Brand et al., 2000) is unknown. Duration tuning arises from precise temporal interactions of inhibition and excitation generated by a single tone (Casseday et al., 1994; Fuzessery and

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Abbreviations: A1, primary auditory cortex; AAF, anterior auditory field; AP, all-pass; BP, band-pass; BW, bandwidth; CF, characteristic frequency; DSI, direction selectivity index; FP, fast-pass; FM, frequency modulated; MT, minimum threshold; P, postnatal day; RTI, rate tuning index; SP, slow-pass.

* Corresponding author. Tel.: +1 951 827 5060.
E-mail address: khaleel@ucr.edu (K. Razak).

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Hall, 1999). Whether duration tuning changes during development is unknown in any species, and such studies will provide insights on the development of temporal interactions. We studied the development of frequency and duration tuning between P15–90 in the core auditory cortex of mice.

The second goal was to investigate the development of selectivity for frequency modulated (FM) sweeps. FM sweeps are relatively simple sounds to investigate basic mechanisms and development of spectrotemporal selectivity. FM sweeps are ubiquitous components of vocalizations, including human speech and rodent calls. Both rate and direction of change of frequencies are relevant cues in discrimination of vocalizations (Vignal and Mathevon, 2011; Zeng et al., 2005). Physiological and behavioral studies show sensitivity to FM sweeps in rodents (Wetzel et al., 1998; Zhang et al., 2003). The auditory cortex is necessary for behavioral FM sweep discrimination in rodents (Ohl et al., 1999). In both bats and chinchillas, FM sweep rate selectivity is adult-like at the time of hearing onset, but FM direction selectivity develops slowly (Brown and Harrison, 2010; Razak and Fuzessery, 2007a). A recent study of the core auditory cortex of mice demonstrated strong FM rate selectivity (Trujillo et al., 2011), but it is not known whether this selectivity is developmentally regulated. This study investigated the development of FM sweep rate and direction selectivity between P15 and P90 in A1 and AAF of the C57 mice. Results indicate that the core auditory cortex of C57 mice is not adult-like until around P30. The significant developmental changes observed were sharper frequency tuning and changes in selectivity for FM sweep rates between P15 and P30. There was a moderate but significant change in FM sweep direction selectivity and no observable change in duration tuning for tones.

2. Methods

The Institutional Animal Care and Use Committee at the University of California, Riverside approved all procedures. Mice (C57bl/6J strain, henceforth referred to as C57) were obtained from an in-house breeding colony that originated from breeding pairs purchased from Jackson Laboratory (Bar Harbor, Maine). Mice were weaned at P21 and housed with 2–3 littermates under a 12/12 h light/dark cycle and fed *ad libitum*. Three age groups were studied: P15–20 (17 mice), P21–30 (18 mice), P31–90 (34 mice).

2.1. Justification of mouse strain and for pooling data from P31–P90 as the adult group

The C57 strain was chosen because it is a commonly used background strain for many genetic models of disease with auditory communication disorders (e.g., presbycusis, Fragile X Syndrome). The data from this study can serve as the baseline for available disease models. This mouse strain shows accelerated age-related hearing loss with audiometric evidence for hearing loss from around P90 (Henry and Chole, 1980; Hunter and Willott, 1987; Mikaelian, 1979; Spongr et al., 1997; Willott, 1986). Comparison of cochlear morphology, auditory brainstem responses and distortion-product otoacoustic emissions shows that the C57 strain is similar to the CBA/CaJ strain at 1 month, and begins to deviate at 3 months (Park et al., 2010). Auditory cortical responses and gross tonotopy appear to be normal in the 1 month old C57 mice and start to show plasticity from 3 months of age (Willott et al., 1993). Taberner and Liberman (2005) compared auditory nerve fiber responses between C57 (~4 month) and CBA strains (age between 2 and 4 month) and found no differences in spontaneous rates, tuning curves, rate *versus* level functions, dynamic range, response adaptation, phase-locking, and the relation between spontaneous rate and response properties. The only difference found in the 4 month old C57 mice was the expected elevation in high-frequency hearing threshold. Trujillo et al. (2011) showed no differences in cortical FM sweep selectivity between 1–2 mo old mice and 2–3 mo old mice. Taken together, these studies show most changes in the C57 auditory system compared to the CBA strain begins to happen around 3 months of age and becomes more pronounced between 3 and 6 months. Therefore, the data for adult mice (ages between P31 and P90) were pooled.

2.2. Surgical procedures

Mice were anesthetized with i.p. injections of ketamine (150 mg/kg) and xylazine (10 mg/kg) mixture. Anesthetic state was monitored throughout the experiment using the toe-pinch reflex test and supplemental dose of the ketamine/xylazine mixture was given as needed. Once an areflexic state of anesthesia was reached, a scalp incision was made along the midline, the skull was cleaned and a craniotomy was performed. The auditory cortex was exposed based on skull and vascular landmarks identified in Willott et al. (1993). Acute electrophysiology recordings were performed on each mouse.

2.3. Acoustic stimulation

Acoustic stimulation and data acquisition were driven by custom written software (Batlab, developed by Dr. Don Gans, Kent State University) and a Microstar digital signal processing board. Programmable attenuators (PA5, Tucker-Davis Technologies, Florida) allowed control of sound intensities before amplification by a stereo power amplifier (Parasound, HCA1100) or an integrated amplifier (Yamaha AX430). Sounds were delivered through a free field speaker (LCY-K100 ribbon tweeters, Madisound, Wisconsin) located 6 inches and 45° from the left ear, contralateral to the recording site. Frequency response of the sound delivery system was measured using a ¼ inch Bruel and Kjaer microphone and measuring amplifier and found to be flat within ±3 dB for frequencies between 7 and 40 kHz. Frequencies <5 kHz were filtered out (Butterworth, 24 dB/octave, Krohn-Hite).

2.4. Electrophysiology

Mice were placed in a Kopf stereotaxic apparatus (model 930, Tujunga, CA) and secured in a mouse bite-bar adapter (Kopf model 923B). Experiments were carried out in a heated (~80 °F), sound-attenuated chamber lined with anechoic foam (Gretch-Ken Industries, Oregon). Electrophysiological recordings were obtained with glass electrodes filled with 1M NaCl (2–10 MΩ impedance). Electrodes were driven orthogonally into the cortex using a Kopf direct drive 2660 micropositioner. Single unit recordings were obtained between 100 and 700 μm from the cortex surface, with ~90% of neurons recorded between 200 and 500 μm. For depth measurements, ‘zero’ was defined as the point when the electrode first touched the surface of the cortex indicated by changes in recording trace and audio monitor output. The consistency of the zero point was also verified when the electrode was pulled out from a penetration. Single unit recordings were identified by the constancy of amplitude and waveform displayed on an oscilloscope and isolated using a window discriminator. Poststimulus time histograms were obtained relative to stimulus onset. Action potentials that occurred within 400 ms of stimulus onset were included in the poststimulus time histograms. The number of spikes that were elicited over 20 stimulus repetitions was used for quantification of response properties. There was no spontaneous activity in the vast majority of recordings. In a few neurons with spontaneous activity, the response of the neuron in the absence of stimulus over the 400 ms