LATENCY AND AMPLITUDE DIFFERENCES IN ABR WAVE PATTERNS OF KCNA1 NULL-MUTANT AND WILD-TYPE MICE

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Introduction
The auditory brainstem evoked response (ABR) recorded from surface electrodes consists of a regular series of five brief waves and less pronounced additional wavelets that occur within the first 10 ms of stimulus onset. The compact form of any one of these ‘peaks’ suggests its basis in the near-synchronous firing of a population of homogeneous neurons (Melcher et al. 1996), while the overall development of the series of peaks is thought to reflect the serial and parallel progression of neural transmission from cells of the spiral ganglion and the auditory nerve, through the cochlear nucleus and the superior olivary complex, to thelemniscal nuclei and the inferior colliculus (in mice, Henry, 1979).

The Kv1.1 channel controls a fast acting low threshold rectifying potassium current that limits the duration of subthreshold EPSPs and leads to neural responses that are selective for synchronous synaptic input. In slice preparations pharmacological blockade of this conductance by 4-AP makes octopus cells more excitable and increases their temporal variability (Bal and Oertel, 2001). Also, a loss of synaptic potassium current is evident in the bushy cells of the ventral cochlear nucleus (Manis and Marx, 1991) and in MNTB cells (Brew and Forsythe, 1995), both of which are thought to make important contributions to the ABR waveform (Melcher et al. 1996).

The relative abundance of Kv1.1 in the auditory brainstem, and its apparent critical role in the normal function of cell-types implicated in ABR generation suggest that KCNA1 (Kv1.1) KO mice may show abnormalities in the timing and amplitudes of the ABR component peaks, reflective of deficits in the high-fidelity transmission of auditory information in the mouse brainstem.

Methods
SUBJECTS:
The subjects were 18 wild-type and 12 KCNA1 null-mutant knock-out (KO) mice of the C3H6HeJ strain, born and raised in the Rochester vivarium, the offspring of heterozygotic parents derived from stocks originally obtained from the Jackson Laboratories. They were tested at 16-18 days of age.

APPARATUS AND PROCEDURE:
ABR audiograms were measured in response to tone bursts (6, 12, 16, 24, 32, and 48 kHz) presented at the rate of 11 bursts per second. Tone duration was 1 ms with a 0.5 ms Blackman windowed start/stop time. Stimulus level ranged from 90 dB SPL (60 dB at 48 kHz) to 20 dB SPL (60 dB at 48 kHz) in 5 dB steps, the loudspeaker (Panasonic TDH100; effective bandwidth 1-100 kHz) located at 0°, and the subject in the supine position. The sound was delivered to the right ear through a 1/8″ earphone (T20) sealed against the pinna with a rigid cover to mask extraneous sound. Stimuli were terminated by a 100 ms noise burst. The sound intensity was monitored with a Bruel & Kjaer 2201 sound levelmeter (Bruel & Kjaer Model 4190) placed at the location of the meatal opening of the pinna. The ABR was recorded with subcutaneous platinum needle electrodes placed at the vertex (non-inverting input), right and left mastoid (inverting input) and left hind limb (reference). The ABR was amplified by a Newport computerized audiometer AS-1 and was monitored on a medical grade dual踪 sound levelmeter (Grason Stadler 3280) and onto a computer hard disk for offline analysis. ABR data were analyzed using neural waveforms software (NeuralWave Systems, Inc., San Diego, CA) and the latency data.

Group Mean Amplitudes and Differences (+/- 95% CI):
90 dB SPL 3-32 kHz
Latency (ms) 16 kHz, 90-40 dB SPL
16 kHz, across level.

Peak latencies (M +/- SEM)
Summary of Results
The overall wave patterns were the same in both groups, but significant differences are apparent in both the amplitude and the latency data. Amplitudes and latencies of P1 (auditory nerve) were near identical in KO and WT mice, but the KO mice showed a persistent level-dependent positivity. This difference between the groups was largest in the troughs lying between the peaks, and was also present in the early ascent to P1 (see the significant regions in C1 functions). Single-trace peak latencies were scored by eye-assisted software (both naïve to group identity) and are subject to confusion between waves and wavelets; none of the less, these unbiased data show that later peaks were faster in KO mice (p<.05). Hearing thresholds were similar in the two groups, save that KO mice showed a 10 dB greater sensitivity for P1 at 3 kHz.

Discussion
Modest differences in P1 development suggest a small AN effect, the later differences indicating more substantial VCN bushy cell and possibly SOG involvement. These findings support prior in vitro work in showing increased excitability in Kv1.1 KO mice, consistent with a slower return to a baseline resting potential.

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