Role of Connexin 43 and Hearing Loss: Possible Connection to Auditory Neuropathy

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INTRODUCTION

Mutations in genes encoding gap junctional proteins in the inner ear account for approximately half of the genetic hearing loss (1,2). Gap junctions, comprised of connexin (Cx) proteins, are sites of intercellular coupling that are involved in tissue growth and differentiation, cell signaling, and ion recycling. It is believed that gap junctions play a critical role in embryogenesis, as evidenced by the lethality of Cx43 knockout (KO) mice and cardiac malformations and ventricular arrhythmia in Cx43 heterozygote (HT) mice (3). Mutations in the gene encoding Cx43 are associated with auditory dysplasia, a developmental disorder characterized by craniofacial and limb dysmorphism, neurologic abnormalities, and hearing loss (4). Cx43 is widely expressed throughout the central nervous system (5,6) and displays transient developmental changes in expression that suggest a role in postnatal development (7). The role of potentially important Cxs other than Cx26 and Cx30 in inner ear development and function remains largely unknown. The present study explores the distribution of Cx43 along the retrocochlear auditory pathway using FluoroGold (FG) (8) as a retrograde tracer in both CBA and Cx43 transgenic mice. Effect of Cx43 mutation on auditory function will also be assessed using auditory brainstem response (ABR) testing.

METHODS AND MATERIALS

Mice: CBA (normal hearing mice), Cx43 heterozygote (HT) and wild type littermates (WT) were tested at several time points (minimum N of 3)

ABR Testing: The stimuli consisted of clicks delivered via soundfield presentation in decreasing sound intensity levels from 80 dB down to 5 dB at 5 dB intervals. Responses were recorded through electrodes placed subcutaneously on the vertex and in the bilateral retroauricular regions. Threshold was defined as the intensity level with the last response at the wave V amplitude. Measurements were recorded and analyzed with a Tucker Davis Technologies (TDT) S3 ABR system (Alachua, FL).

DISCUSSION

The cellular localization of specific Cx subtypes provides a basis for understanding the mechanism of hearing loss. The molecular mechanism responsible for hearing loss due to mutations in Cx26 and Cx30 genes is theorized to be due to leaky gap junction (GJ) hemichannels, resulting in cell-to-cell uncoupling (9). Electrical synaptic transduction via GJs is a well-known mode of interneuronal communication in the central nervous system (10). In another sensory system such as the visual system, GJs provide direct electrical signaling between cells in the retina (11). A similar mode of synaptic transmission may be found in the auditory system.

CONCLUSIONS

To our knowledge, this is the first study to evaluate the impact of Cx43 in the murine inner ear development and function using Cx43 mutant mice. Our study suggests that while Cx43 mutations do not affect inner ear development, they play an important function in maintaining auditory function with aging. The precise mechanism of hearing loss resulting from mutations in these proteins is not completely understood at this time, but from their cellular localization, premature elevated ABR thresholds associated with abnormal waveforms, the possibility of auditory nerve dysynchrony in the retrocochlear auditory pathway is proposed.

REFERENCES