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Contribution of Auditory Nerve Nodal Structural Refinement to Postnatal Maturation of Mouse Auditory Function

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Proper passage of electrical impulses and regulation of conduction velocity through the auditory nerve (AN) fibers are necessary for normal auditory function. Myelinating glia cells ensheath type I spiral ganglion neurons (SGNs) with multiple layers of myelin. This sheathing provides electrical insulation, which helps sustain the strength of traveling action potentials along the fiber. Nodes of Ranvier, formed in part by unmyelinated gaps and the terminal ends of myelin sheaths, are necessary for the regeneration of action potentials throughout the length of the type I SGN. Our lab has previously shown that glial dysfunction resulting from dysregulation of *quaking,* a regulator of myelination, contributes to noise-induced hearing loss. We further determined that knocking out *quaking* in adult mice causes demyelination and abnormalities in nodal structures, which are associated with elevated auditory brainstem response (ABR) thresholds and delayed wave I latencies. Studies about the role of the nodal structures during the emergence of hearing function have been sparse. Here we aim to elucidate the role of nodal structural refinement in hearing onset and AN functional maturation of the developing mouse ear.

We used postnatal (P) CBA/CaJ mice ages P3-P21 and 1 month in our experiments. In our study, we identified and characterized for the first time three types of excitable nodal structures in the mouse AN, showing how these nodal structures form and refine during postnatal cochlear development around the critical period of hearing onset and hearing maturation. The two types of myelinating glial cells in the mouse AN, Schwann cells and satellite glial cells, form structurally different excitable nodal structures, which may result in differing electrical properties between the node types. To determine how nodal structural maturation contributes to the maturation of AN function, we examined the extent to which the changes in nodal lengths were associated with measurements of AN function in postnatal mice (from P14 to P21). AN function maturation was determined by quantifying neural synchrony *in vivo* with comprehensive analysis of ABR metrics such as wave I amplitude, latency, and pure-tone thresholds. Our results demonstrate that refinement of nodal structures, especially that of the nodes formed in part by the satellite glial cells, are significantly associated with maturation of the AN function. This work was supported by grants from the NIH/NIDCD.

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Optical Coding Using Photopharmacological Stimulation of Ionotropic Glutamate Receptors in Spiral Ganglion Neurons

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Light stimulation of spiral ganglion neurons (SGNs) in the ear provides a future alternative to electrical stimulation used in cochlear implants. Optogenetic manipulation of neuronal activity is based on the expression of light-sensitive proteins, which requires gene therapy. An alternative to optogenetics is offered by photopharmacology which operates on endogenous receptors and does not require genetic manipulation. Among the "photoswitches", the Targeted Covalent Photoswitches (TCP) mainly reacts with the ionotropic kainate receptor GluK1. It was previously shown *in vitro* on hippocampal neurons that TCP9, the best first-generation compound, activates native GluK1 receptor upon ultraviolet light (380 nm) and a deactivates the receptor upon visible light (500 nm, Volgraf et al., 2006). In this study, we tested a new generation of blue-shifted TCP *in vivo* by applying the compound to the gerbil cochlea via the round window. Electrocochleography via a round window niche electrode showed us a preservation of the acoustically-evoked cochlear microphonic and compound action potential (CAP) amplitude, indicating that the compound and its binding to glutamate receptors does not alter cochlear function. Upon light stimulation using an optical fiber (β = 473 nm), we observed optically evoked CAPs (oCAPs). oCAPs could be evoked by light pulse radian flux as low than 3 mW, oCAP amplitudes were maximum in response to 80 µs light pulse and were sizable up to a repetition rate of 4 kHz. This performance makes this compound an interesting tool for optical SGN stimulation. Future experiments will investigate the single unit response of light evoked auditory nerve fiber and hearing restoration on a deafness model.

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Neural crest and placode contributions to congenital deafness in Waadenburg-Shah syndrome

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Waardenburg-Shah syndrome is a congenital deafness that is associated with Hirschsprung disease. In human,