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A Mouse Model of the Auditory Nerve to Study Cochlear Synaptopathy

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Introduction

Several non-human animal studies have demonstrated a perennial loss of auditory nerve (AN) fiber synapses after noise over-exposure, termed cochlear synaptopathy, without causing hair cell loss or altering normal auditory thresholds (e.g., Rujasz and Liberman, 2009). Studies in humans are generally inconclusive, mainly because hearing testing of the AN in humans represents a major challenge. In a previous study, we proposed the use of envelope following responses (EFR) as a tool to investigate synaptopathy both in mice and humans (Encina-Llamas et al., under review; Parthasarathy et al., 2017). Similar patterns of synaptopathic mice and humans were found. The use of a “humanized” version of the AN model by Zilany et al. (2009, 2014) could qualitatively account for the patterns observed in the human listeners. Nevertheless, the use of the original animal version of the AN model (based on the cat) failed to simulate EFRs in mice. It was argued that a species-specific AN model could improve the non-human animal simulations. Given that the mouse is the most used and best characterized species in connection with cochlear synaptopathy, the present study proposes a modification of the original AN model by Zilany et al. (2009, 2014) based on cat data adapted to the mouse.

Aim of the project

• Modify the AN model by Zilany et al. (2009, 2014) based on the cat to adapt it to the mouse.
• Due to the complexity of the AN model, it was intentionally decided to modify as few parameters as possible.
• Three main blocks were modified: the middle-ear filter, the cochlear tuning (Q0.5a.u. values), and the range of sensitive characteristic frequencies (CF).
• The ultimate goal was to use the model to simulate EFRs in non-synaptopathic and synaptopathic mice.

Methods

Model: • Modified” version based on the AN model by Zilany et al. (2009, 2014).
• 29 characteristic frequencies (CF): Mangold 4 to 5 kHz.
• Synapses per CF are simulated by independent, independent synapses of each 8 kHz (8 kHz fibers per CF) with a total of synapses.
• Synaptology is simulated by computing a 2D red (synaptic) layer (stimulus) and the model with synaptic (gray, lines) and synaptopathic (gray, dashed lines) levels using strongly (blue) and weakly (red) modulated tones.

Results I

EFRs recorded in mice:

• Non-synaptopathic (f = 12.1 kHz, 100 dB SPL)
• Synaptopathic (f = 12.1 kHz, 100 dB SPL)

Simulated EFRs using the CAT model:

• Non-synaptopathic (f = 2.8 kHz, 100 dB SPL)
• Synaptopathic (f = 2.8 kHz, 100 dB SPL)

Simulated EFRs using the MOUSE model:

• Non-synaptopathic (f = 12.1 kHz, 100 dB SPL)
• Synaptopathic (f = 12.1 kHz, 100 dB SPL)

Analysis on- and off-frequencies and different fiber types:

• Analysis on- and off-frequencies and different fiber types.

Conclusion

• The modifications applied to “human” the AN model (IE fiber tuning and range of sensitive CFs) were sufficient to generally account for the mouse AN thresholds.
• The mouse model improved significantly the simulation of EFR-level growth functions in mice with respect to the use of the cat model.
• Although the model simulations capture the general trend of the EFR-level growth functions, there are still discrepancies in particular at the lower and higher stimulus levels at the synaptopathic frequency.
• Simulated EFRs using the mouse model at supra-threshold levels are dominated by the activity of high-SR fibers at off-frequency contributions, similarly to the humanized AN model (Encina-Llamas et al., under review).

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