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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 persistent loss of auditory nerve (AN) fiber synapses after noise overexposure, termed cochlear synaptopathy, without causing hair cell loss or altering normal auditory thresholds (e.g., Kujawa and Liberman, 2009). Studies in humans are generally inconclusive, mainly because of using the status of the AN in humans represents a major challenge. In a previous study, we proposed the use of evoked frequency responses (EFRs) 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 and healthy 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 obtained 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 (Q10 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

- "Mousification" of the AN model
- The modifications applied to "mousify" the AN model (ME) are the 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 synapticopathic 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).

Results I

- EFRs recorded in mice:
  - Non-synaptic frequency: (fcat = 12.1 kHz) (CF at 30.49 kHz)
  - Synaptic frequency: (fcat = 12.1 kHz) (CF at 50 kHz)

Simulated EFRs using the CAT model:

Simulated EFRs using the MOUSE model:

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

Results II

Conclusion

- The modifications applied to "mousify" the AN model (ME) 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 synapticopathic frequency.
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References

- Dong et al. (2014). JASA, 131(2), 407-421. DOI: 10.1121/1.4887748.

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