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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 permanent loss of auditory nerve (AN) fiber synapses after noise over-exposure, termed cochlear synaptopathy, without causing hair cell loss nor altering normal auditory thresholds (e.g., Rujas and Liberman, 2009). Studies in humans are generally inconclusive, mainly because of the confounding status of the AN in humans represents a major challenge. In a previous study, we proposed the use of evoked-response potentials (ERPs) as a tool to investigate synaptopathy both in mice and humans (Encina-Llamas et al., under review; Parbasanyan et al., 2017). Similar patterns of synaptic loss in rats and mice 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 data to adapt it to the mouse.
- Due to the complexity of the AN model, it was intentionally decided to modify it as few parameters as possible.
- Three main blocks were modified: the middle-ear filter, the cochlear tuning (Q10dB values), and the range of sensitive characteristic frequencies (CF).
- The ultimate goal was to use the model to simulate EFRs in non-synaptopathic and synaptic mice.

METHODS

“Mousification” of the AN model

- Simulated AN EFR level-growth functions using the CAT model at the non-synaptopathic (Panel A, $f_c = 0.29$ kHz) and synaptic (Panel B, $f_c = 0.39$ kHz) levels for exposed (circles, dashed lines) and non-synaptopathic (squares, solid lines) mice using strongly (blue) and shallowly (red) modulated tonal stimuli.
- For more information, refer to the following source: Encina-Llamas et al. (2020).

RESULTS I

- The modifications applied to “mousify” the AN model (IE fiber tuning and range of sensitive CFs) were sufficient to 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 trends of the EFR level-growth functions, there are still discrepancies in particular at the lower and higher stimulus levels at the synaptic characteristic frequencies.
- Simulated EFRs using the mouse model at supra-threshold levels are dominated by the activity of high-SR fibers at off-frequency contributions, similar to the humanized AN model (Encina-Llamas et al., under review).

AN tuning:

- The model simulates the AN tuning by comparing the original AN tuning (black) in the mouse model.
- The solid lines correspond to the original AN tuning in the mouse model.
- The dashed lines represent the AN tuning in the humanized model.
- The 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.

AN thresholds:

- Simulated AN thresholds for exposed (circles, solid lines) and non-synaptopathic (squares, dashed lines) mice using strongly (blue) and shallowly (red) modulated tonal stimuli.
- For more information, refer to the following source: Encina-Llamas et al. (2020).

Conclusion

- The modifications applied to “mousify” the AN model (IE fiber tuning and range of sensitive CFs) were sufficient to 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 trends of the EFR level-growth functions, there are still discrepancies in particular at the lower and higher stimulus levels at the synaptic characteristic frequencies.
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References


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