A mouse model of the auditory nerve to study cochlear synaptopathy

Encina-Llamas, Gerard; Dau, Torsten; Harte, James Michael; Epp, Bastian

Publication date: 2018

Document Version
Publisher's PDF, also known as Version of record

Link back to DTU Orbit

Citation (APA):
A Mouse Model of the Auditory Nerve to Study Cochlear Synaptopathy

Gerard Encina-Llamas¹, Torsten Dau¹, James M. Harte² and Bastian Epp¹

¹ Hearing Systems, Technical University of Denmark (DTU) - ² Interacoustics Research Unit (IRU)

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 or altering normal auditory thresholds i.e., Rajasek and Liberman, 2009). Studies in humans are generally inconclusive, mainly because assessing the status of the AN in humans represents a major challenge. In a previous study, we proposed the use of evoked temporal 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 synaptic loss in AN and the mouse 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 (Qo, 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:
• “Mousified” version based on the AN model by Zilany et al. (2009, 2014): 200 characteristic frequencies (CF); 30-20000 Hz; 5 CF per octave; each CF has 200 fibers per CF of a given CF less times..
• Synaptic per CF are simulated by independent synapses of each CF (30-2000 fibers per CF of a given CF less times).
• Synaptically is simulated using a simplified 2nd order IIR filter in Bruce Taberner & Liberman, 2005) and fitted line are represented in green.

Simulated EFRs using the CAT model:
• Non-synaptopathic (Panel A, f = 12.1 kHz; 0.65 kHz frequency response, 30 % of the first harmonic, solid line) and the model with synap- tic loss (dashed line) using strongly (blue) and shallowly (red) modulated tones.
• More information, attended to the podium PD et al., 2013).

Simulated EFRs using the MOUSE model:
• Non-synaptopathic (Panel A, f = 12.1 kHz) and synaptopathic (Panel B, f = 13.9 kHz) frequency response, 30 % of the first harmonic, solid line) and the model with synap- tic loss (dashed line) using strongly (blue) and shallowly (red) modulated tones.

Fig. 8 Simulated EFR level-growth functions using the MOUSE model (Encina-Llamas et al., under review).

Results I

EFRs recorded in mice:
• Non-synaptopathic frequency (f = 12.1 kHz; CF at 30.4 kHz) and synaptopathic (Panel B, f = 13.9 kHz) frequency response, 30 % of the first harmonic, solid line) and the model with synap- tic loss (dashed line) using strongly (blue) and shallowly (red) modulated tones.

“Mousification” of the AN model

Middle-ear filter:
• Non-nonsynaptopathic frequency (f = 2.2 kHz; solid line) and (dashed line) using strongly (blue) and shallowly (red) modulated tones.
• More information, attended to the podium PD et al., 2013).

AN tuning:
• AN tuning – CAT (middle-ear filter - Phase)
• AN tuning – MOUSE middle-ear filter - Magnitude

Analysis at on- and off-frequencies and different fiber types:
• Analysis at on- and off-frequencies and different fiber types: High-SR fibers

Conclusion

• The modifications applied to “mousify” the AN model (ME) 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).

References

Bruce et al. (2009), JASA 126(1), 52-71. DOI: 10.1121/1.3125058
Dong et al. (2012), JASA 132(6), 2671-2677. DOI: 10.1121/1.4742373
Garwood et al. (2014), JASA 136, 42-53. DOI: 10.1121/1.4869402
Weller et al. (2015), JASA 138, 3886-3899. DOI: 10.1121/1.4924833
Parthasarathy et al. (2016), JASA 140, 78-89. DOI: 10.1121/1.4945029
Domar et al. (2016), JASA 140, 2136-2154. DOI: 10.1121/1.4962783
Zilany et al. (2009), JASA 126, 2667-2682. DOI: 10.1121/1.3192302
Zilany et al. (2014), Hearing 2014, 1-8. DOI: 10.1121/1.4916203
Zilany et al. (2017), Hearing 2017, 1-8. DOI: 10.1121/1.4992828
Zilany et al. (2018), JASA 143, 2020-2040. DOI: 10.1121/1.5017588

Acknowledgements

This research was supported by the Danish Centre for Excellence for Hearing and Speech Sciences (CHeSS) at the Technical University of Denmark (DTU).