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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) fibers synonymous after noise over-exposure, termed cochlear synaptopathy, without causing hair cell loss nor altering normal auditory thresholds (e.g., Rajasek and Liberman, 2008). Studies in human listeners 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 field responses (EFRs) as a tool to investigate synaptopathy both in mice and humans (Encina-Llamas et al., under review; Parribasanz 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 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.

**Methods**

- **Model:**
  - "Modified" version based on the AN model by Zilany et al. (2009, 2014).
  - 298 characteristic frequencies (CFs) ranging 4 to 8 kHz.
  - Synapses per CF are simulated by 298 independent synapses of each AN CF (30-60 fibers per CF with a total of 55500 fibers).
  - Synaptic delay is simulated computing a 298th-order section structure.

- **Simulated EFRs using the CAT model:**
  - Non-synaptopathic (Panel A, f = 12.1 kHz) and synaptopathic (Panel B, f = 12.1 kHz) frequencies for exposed (circle, solid line) and synaptopathic (square, dashed line) mice using strongly (blue) and shallowly (red) modulated tones. For more information, attend to the radiodiod J. Neurophysiol. 93(1), 557-69.

- **Simulated EFRs using the MOUSE model:**
  - Non-synaptopathic (Panel A, f = 12.1 kHz) and synaptopathic (Panel B, f = 12.1 kHz) frequencies for exposed (circle, solid line) and synaptopathic (square, dashed line) mice using strongly (blue) and shallowly (red) modulated tones.

**Results I**

**Simulated EFRs recorded in mice:**

- **EFRs recorded in mice:**
  - **Non-synaptopathic frequency (f_{NS})**:
    - EFR magnitude
  - **Synaptopathic frequency (f_{S})**:
    - EFR magnitude

**Simulated EFRs using the CAT model:**

- **Stimuli:**
  - Non-synaptopathic frequency (f_{NS}) = 12.1 kHz @ 30 dB SPL
  - Synaptopathic frequency (f_{S}) = 12.1 kHz @ 30 dB SPL

**Simulated EFRs using the MOUSE model:**

**Analyze on- and off-frequencies and different fiber types:**

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

**Conclusion**

- The modifications applied to “mousify” the AN model (IEF is part) 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 models 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, 120(3), 1446-1466
- Dong et al. (2018), Hear Res, 358, 227-241
- Liberman et al. (2015), JASA, 138(3), 1211-1231
- Liberman et al. (2010), JASA, 127(4), 2197-2212
- Lenaerts et al. (2001), JASA, 110(6), 3055-3072
- Liberman et al. (2001), JASA, 110(3), 1040-1054
- Pohlen et al. (2000), JASA, 108(3), 1493-1508
- Taberner et al. (2003), Lab. Noise Control 7, 20-27
- Yoshida et al. (2000), Hear Res, 147(1-2), 193-208
- Yoshida et al. (2001), JASA, 109(6), 3228-3240
- Yoshida et al. (2001), JASA, 109(6), 3228-3240
- Yoshida et al. (2003), JASA, 114(6), 3256-3268
- Yoshida et al. (2005), JASA, 117(4), 1051-1063
- Yoshida et al. (2007), JASA, 122(3), 1560-1568
- Yoshida et al. (2009), JASA, 125(3), 1353-1363
- Zilany et al. (2006), JASA, 120(3), 1446-1466

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