Targeting Oxidative Stress in the Cochlea: Neuroprotective Potential of MP201 in Blast-Induced Hair Cell Damage

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Abstract

Blast trauma elevates reactive oxygen species (ROS) in the cochlea, driving hair cell death and permanent hearing loss. Mild mitochondrial uncoupling reduces ROS and has been shown to be neuroprotective in models of brain and auditory injury. MP201, a prodrug of MP101 (DNP), offers improved pharmacology and has shown promise in noise-induced hearing loss.

In a rat model of repeated blast exposure, MP201 did not yield overall protection but suggested region-specific effects, appearing protective in mid-cochlear regions while potentially detrimental at the base.

Overall, these findings indicate that MP201 may modulate cochlear vulnerability to blast injury in a region-dependent manner, warranting further study to refine its therapeutic potential.

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Background

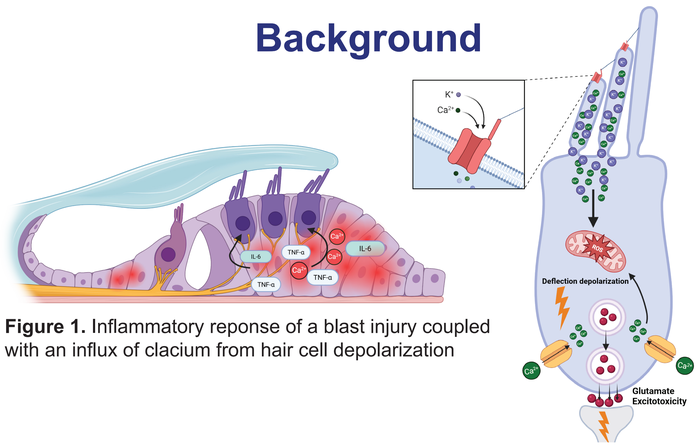


Figure 1. Inflammatory reponse of a blast injury coupled with an influx of clacium from hair cell depolarization

Hypothesis

MP201, a mitochondrial uncoupling prodrug, mitigates cochlear hair cell loss following repetitive blast trauma by reducing oxidative stress.

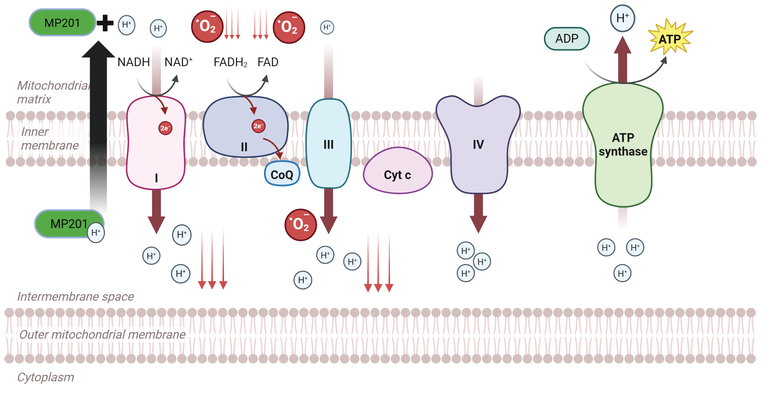


Figure 2. MP201 acts on the Electron Transport Chain (ETC) to reduce free radical generation and the mitochondrial membrane potential responsible for calcium influx and mitochondrial toxicity.

Methods

Multiple blast injury model

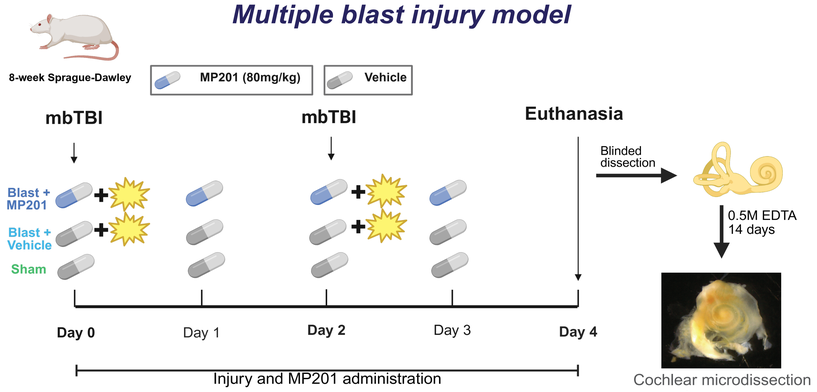


Figure 3. Schematic of drug delivery and blast timeline

Blast device

Figure 4. Blast device showing perforatable (B) membrane and animal location (F). Modified from Reneer et al., Journal of Neurotrauma, 2011.

Tissue processing

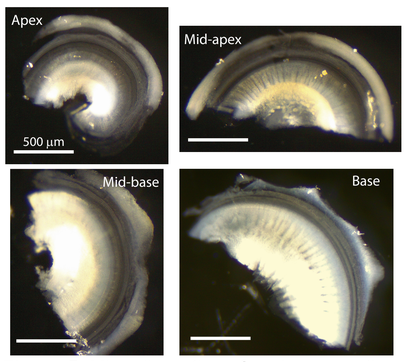


Figure 5. Microdissection of cochlea resulting in four segements of the cochlea

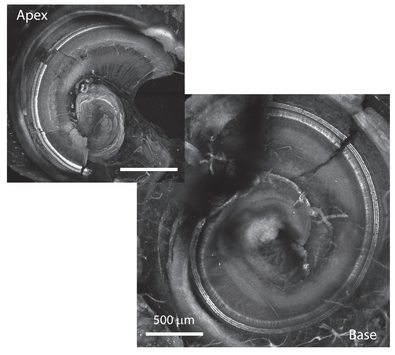


Figure 6. Hemidissected cochlea after tissue clearing and MYO7 labeling

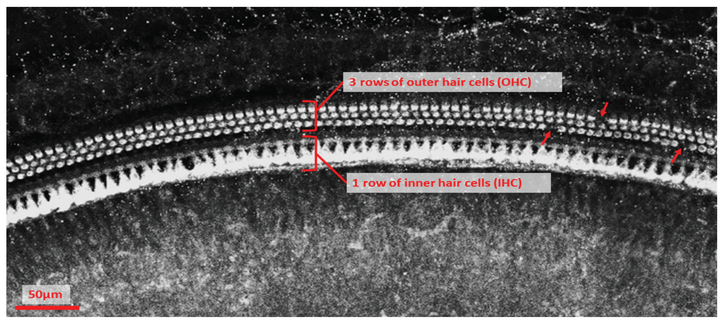
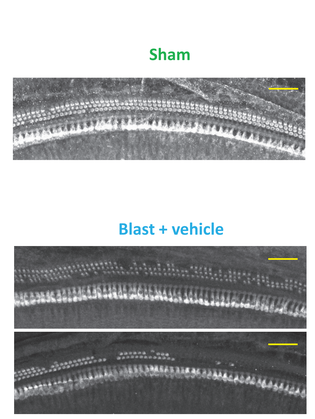


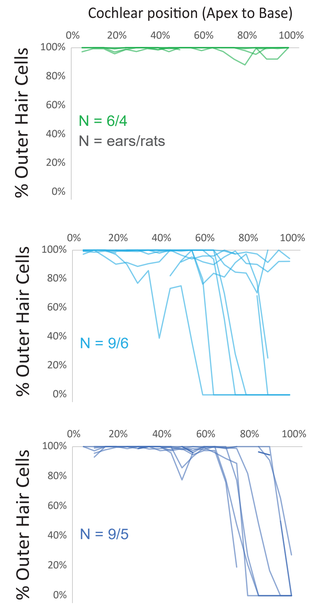
Figure 7. Confocal microscopy image of MYO7-labeled cochlea showing three rows of outer hair cells and one row of inner hair cells with demarcations of missing outer hair cells (red arrows).

Results

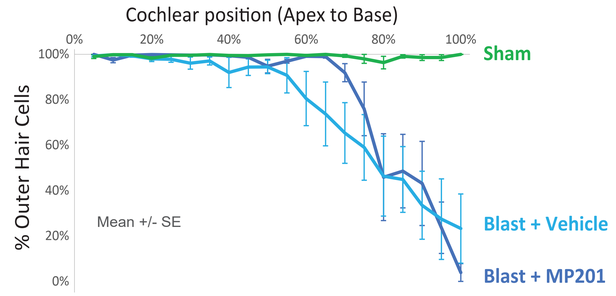
Animals exposed to two blasts and receiving vehicle control show high variability in the degree of hair cell loss



Representative images at 85% cochlear legnth



MP201 failed to significantly protect against multiple blast-induced hair cell loss



Conclusions

- Potential mixed (confounding) effects between MP201 and cochlear location:
  - Protective in mid-cochlear region (60-75% length)?
  - Worsened injury at the base?
- Presence of ears with minimun hair cell loss in vehicle control group could be due to middle ear damage experienced after the first blast, or the presence of larger endogenous "protective" mechanisms (larger threshold shift?) that were minimized in MP201-treated animals

Future Directions

Future studies will refine MP201 dosing/timing, perform hearing tests after the first blast, and assess middle-ear damage between blasts to clarify therapeutic potential of mitochondrial uncoupling.