

## **Therapeutic intervention against excitotoxicity & preservation of cochlear hair cells after noise-trauma induced hearing loss**

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Noise induced hearing loss (NIHL) due to occupational, military and concert exposures is a common cause of hearing impairment that is potentially preventable. It is estimated that about 15% of the United States population (26 million people) between the age of 20 and 69 have NIHL. The aim of the present investigation was to determine the therapeutic effects of mGlu7 negative allosteric modulators (NAMs), developed by PRAGMA Therapeutics, to prevent or reduce hearing loss in CBA/CaJ mice after exposure to loud noise. Although this compound has not been approved for clinical application yet, hearing preservation in treated mice was observed not only for temporary threshold shifts (TTS) but also for permanent threshold shifts (PTS).

Sensory hair cells are essential for auditory processing in the cochlea. Previous studies suggest that noise overstimulation initiates degeneration of the synaptic contacts between inner hair cells and spiral ganglion neurons. Noise overstimulation induces excessive release of glutamate in these synapses causing excitotoxicity together with possible mGlu7 receptor changes, which could be linked to NIHL. The therapeutic compound (PT 145) was administered to anesthetized, young adult mice over a 3-hour period after exposure to an octave band 8-16 kHz signal at 110 dB SPL for 45 minutes. Measured thresholds for auditory brainstem responses (ABR) were elevated by up to 40 dB in controls (noise-exposed, placebo treatment); whereas the treated group showed significantly less PTS, of up to 27 dB when measured 2-weeks post exposure. ABR evaluation 4-weeks post exposure showed larger PTS for the control group (13 dB), relative to the PTS for the treated group, which was only 3 dB. For distortion product otoacoustic emission (DPOAEs), statistically significant differences for TTS occurred for low and medium frequency ranges. Following a recovery period from overstimulation, DPOAE evaluations at 2 and 4-weeks post-exposure within treated groups showed complete recovery to their baseline amplitude level within the low and medium frequency ranges. This striking degree of protection against cochlear noise insults of the NAM agrees with the notion that excessive release of glutamate at the hair cell/auditory nerve dendrite synapses is an important mechanism producing NIHL. Moreover, we have demonstrated that a novel NAM can reduce TTS and PTS after noise exposure, i.e., preserve hearing even when administered after noise overexposure has already occurred.

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