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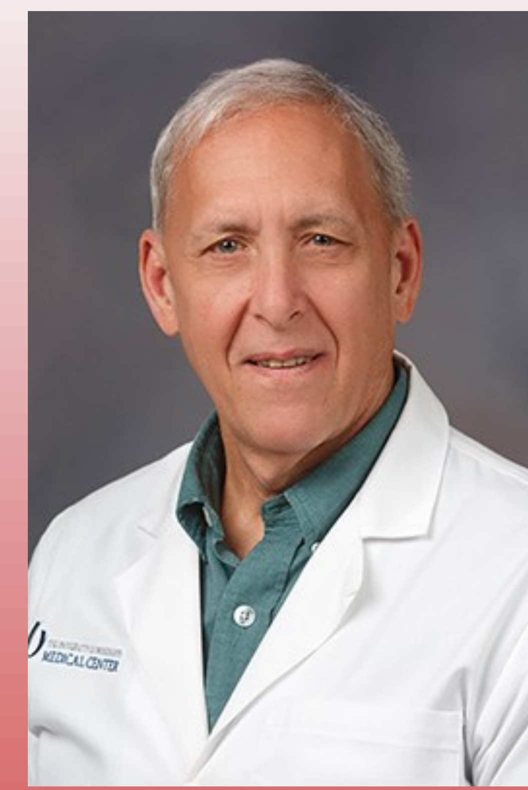

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"Novel Peptidergic Signaling Systems Protective Against Noise-Induced Hearing Loss- A Role for Orexin Signaling in the Mammalian Cochlea"

RESEARCH GRANT 2020

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PUBLICATIONS:

Peptidergic and related steroid signaling in the cochlea:Barnes, CC, Yee, KT, and Vetter, DE (2023) *Conditional ablation of glucocorticoid and mineralocorticoid receptors from cochlear supporting cells reveals their differential roles for hearing sensitivity and dynamics of recovery from noise-induced hearing loss.* Int. J. Mol. Sci. 24(4):3320. doi: 10.3390/ijms24043320. PMID: 36834731

Vetter, D.E. and Yee, K.T. (2018) *Corticotropin Releasing Factor in the Mammalian Cochlea: An Integrative Niche for Cochlear Homeostatic Balance Against Noise.* in: Inflammatory Mechanisms in Mediating Hearing Loss, V. Ramkumar and LP Rybak, eds., Springer Press.

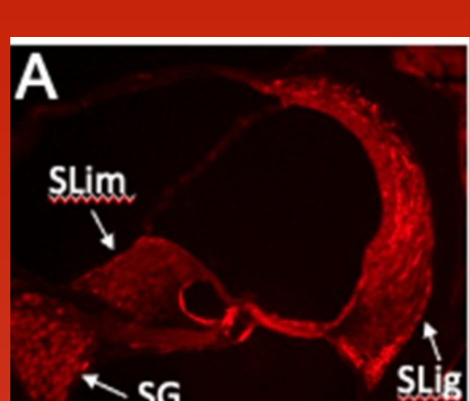
Orexin signaling in the cochlea: Yee, K.T., Ghadiyaram, A., and Vetter, D.E. (in prep) *The role of Orexin A and Orexin B peptides and the Orexin receptor 1 in the mammalian cochlea.*

RESEARCH SUMMARY:

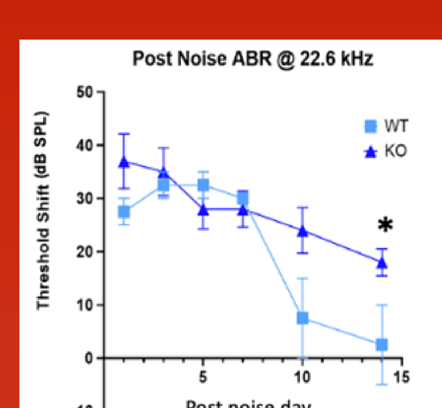
We have used genetic modifications to investigate the role of Orexin signaling in the mouse cochlea. Here, we demonstrate that loss of Orexin receptor 1 (OxR1) gene expression results in greater susceptibility to noise-induced damage at both the physiological and structural levels. Noise exposures that produce mild and temporary elevation of hearing thresholds in normal mice produce a longer lasting and apparently permanent hearing loss in mice lacking the OxR1 gene. Similar research is proceeding to investigate the role of the Orexin R2 gene in noise-induced hearing damage.

OUTCOME:

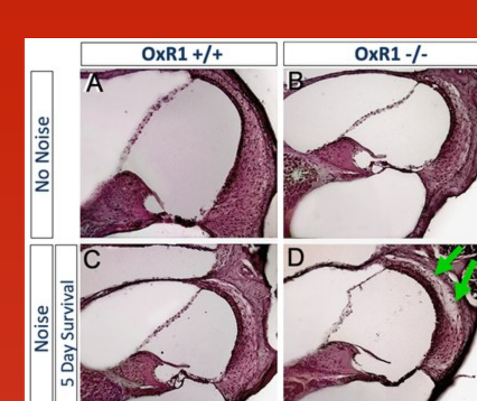
Orexins are hypothalamic peptides typically associated with control over feeding and sleep wake cycles. Orexin receptor (OxR1 and OxR2) antagonists such as Suvorexant (Belsomra®) are marketed to treat insomnia. Orexin receptor antagonist drugs are often taken for much longer periods than prescribed (months to years) for sleep dysfunction, especially by those suffering from anxiety, PTSD, and the general effects of aging. We previously demonstrated peptides normally associated with the hypothalamic function are expressed in the cochlea (Graham et al., 2010, 2011). We asked whether Orexin peptide signaling is present in the cochlea, and if so, whether long-term use of Orexin receptor antagonists might pose an increased risk for hearing loss.



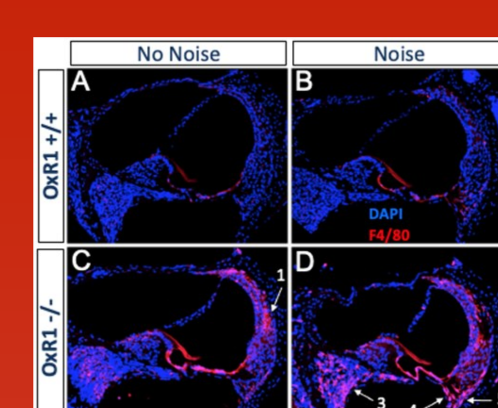
We localized both Orexin peptides (Orexin A and B) to the support cells along the basilar membrane and within the lateral wall of the mouse cochlea (red fluorescence) and both Orexin receptors (OxR1 and OxR2) to the same regions of the mouse cochlea (not shown). (SLim- spiral limbus; SG- spiral ganglion; SLig- spiral ligament)



Using mice with a mutation interrupting OxR1 gene expresson, we demonstrated that exposure to noise intensity normally producing a temporary ABR (wave 1) threshold shift (light blue) in normal mice produces a longer lasting, perhaps permanent, threshold shift (dark blue) in the OxR1 null mice.



Noise also induces a greater degree of damage to the lateral wall in the OxR1 null mice (green arrows) compared to that occurring in wild type mice.



In the absence of noise exposure, F4/80, a marker for macrophages, is higher without noise in the OxR1 null mouse than in controls (cf. C to A). While moderate intensity noise exposure results in F4/80 upregulation in both WT and KO conditions, following noise exposure, marked upregulation of F4/80 occurs in the spiral ganglion (#3 in D), within the spiral ligament in putative type IV fibrocytes (#4 in D) and type III fibrocytes (#5 in D) in OxR1 null mice compared to controls, indicating a greater immune response to noise.

FURTHER FUNDING HAS ENABLED US TO EXPAND OUR RESEARCH TO:

We are developing a full gene expression profile of the major cell types (snRNAseq from baseline and 14 days following noise exposure) of the OxR1 null versus wild type mice. This will advance our understanding not only of the baseline normal response to noise, but also how the Orexin signaling system shapes the cochlea's response to moderate level noise.

LAY SUMMARY OF FINDINGS AND IMPLICATIONS OF THIS RESEARCH:

How the cochlea is protected from the moderate levels of noise intensities typically encountered every day is still incompletely understood. Because the sensory cells (hair cells) of the mammalian cochlea do not regenerate once significantly damaged, there must be a means by which they are protected across our lifetimes, and such protection might stem from metabolic and immunologic support of the inner ear. Our research into the roles of the support (non-sensory) cells of the cochlea has shown that many peptides and their receptors involved with cellular stress responses and metabolic support are critical for protection of normal hearing following exposure to moderate intensity noise. Importantly, the Orexin genes are involved in hearing protection, but this signaling system is also the target of drugs for insomnia. Our research suggests a potential that use of these drugs heightens the potential for hearing loss when exposed to moderately high intensity noise.