P371

NOISE- EXPOSURE

Systemic administration of human umbilical cord perivascular cells reduces noise-induced inflammation in the brain and cochlea in a rat model of noise-induced hearing loss.

Subhendu Mukherjee*, *Ali Mirzaesmaeili, Ayesha Noman, Kajal Patel, Fyyaz Siddiqui, Lianet Lopez, Andree Gauthier-Fisher, Clifford Librach*

*Create Fertility Centre, Sunnybrook Research Institute, University of Toronto, Toronto, Canada (*subhendu@createivf.com)*

Abstract

Sensorineural hearing loss (SNHL), a common sensory impairment in humans, results from damaged hair cells or spiral ganglion neurons. One common cause of SNHL is noise exposure, which leads to noise-induced hearing loss (NIHL). NIHL is a significant health problem in the present era and often remains unrecognized and undertreated. The inner ear was thought to be an immune-privileged organ. However, recent studies have shown that proinflammatory mediators contribute to the NIHL[1-4]. Despite the growing knowledge, there is no specific treatment for SNHL. Recent advancements in regenerative medicine have opened potential cell-based therapies for SNHL. Human umbilical cord perivascular cells (HUCPVCs) are a rich and potent source of MSCs that have anti-inflammatory properties. Our group has characterized first-trimester (FTM) HUCPVC. In this study, we aimed to investigate, in a rat model, noise-induced inflammation in the brain and cochlea in causing NIHL and to determine the use of systemic HUCPVC administration as a potential treatment for this condition.

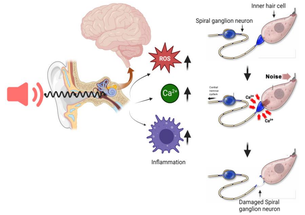


Fig 1. Mechanisms involved in NIHL

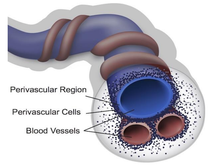


Fig 2. HUCPVC

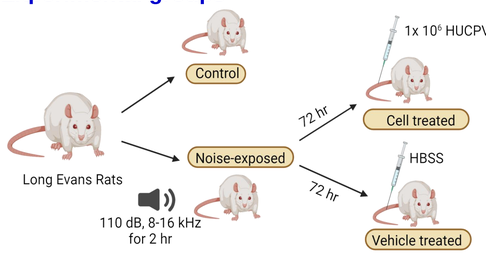
Hypothesis and Objectives

Hypothesis: We hypothesized that noise injury induces inflammation and apoptosis in the brain and cochlea. FTM-HUCPVC treatment can prevent noise-induced inflammation in the brain and cochlea of the NIHL rat model.

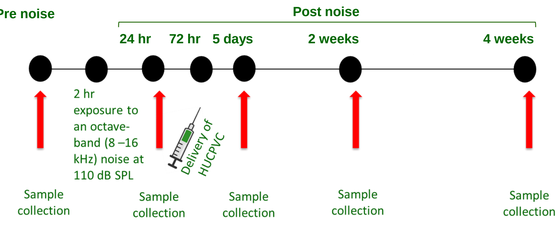
Objective: Our study aimed to assess the noise-induced inflammation and apoptosis markers in the brain and cochlea of noise-exposed rats and check the impact of HUCPVC treatment.

Experimental Methods

Experimental groups



Experimental flowchart



Results

1) Noise exposure damages synaptic ribbons without affecting the inner ear hair cells.

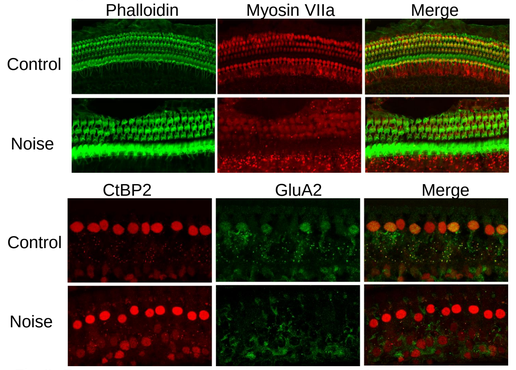


Fig 3. Representative immunostaining images of (A) cochlear hair cells (myosin VIIa, red stain) and hair cell stereocilia bundles (phalloidin, green stain) in the organ of Corti (B) presynaptic and postsynaptic protein pairs (CtBP2 (red stain)/GluA2 (green stain)) in the inner hair cell (IHC) area of control and noise-exposed rats

2) HUCPVC reverse the noise-induced reduction in the levels of the neuronal survival and growth gene (BDNF) in the brain and cochlea

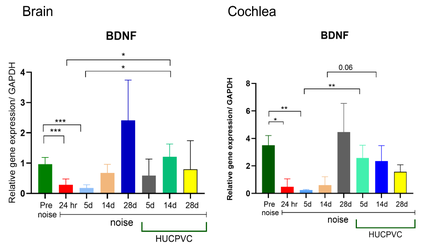


Fig 4. BDNF gene expression in the brain and cochlea of noise-exposed w/wo HUCPVC treated rats. Data presented as mean ± SEM,*p<0.05, **p<0.005, N≥3 per group.

3) HUCPVC can reverse the noise-induced increase of inflammatory gene expression in the cochlea

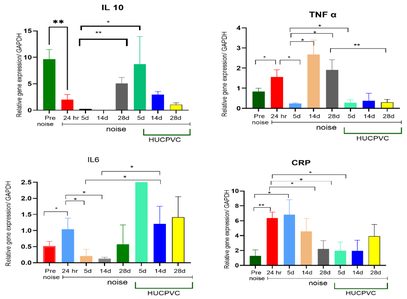


Fig 5. Expression of IL10, TNFα, IL6 and CRP genes in the cochlea of noise-exposed w/wo HUCPVC treated rats. Data presented as mean ± SEM,*p<0.05, **p<0.005, N≥3 per group.

4) HUCPVC treatment reverses noise-induced expression of inflammatory genes in brain tissue

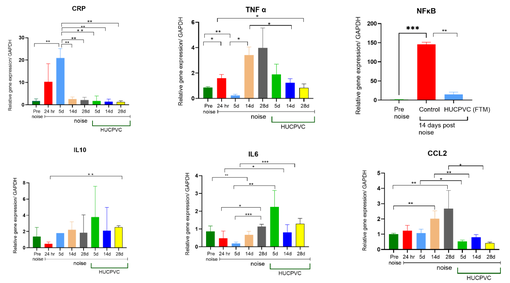


Fig 6. Expression of CRP, TNFα, NFκB, IL10, IL6 and CCL2 genes in the brain tissue of noise-exposed w/wo HUCPVC. Data presented as mean ± SEM,*p<0.05, **p<0.005, ***p<0.0005, N≥3 per group.

5) HUCPVC can reverse the noise-induced increase of the apoptotic and inflammatory protein levels in brain tissue

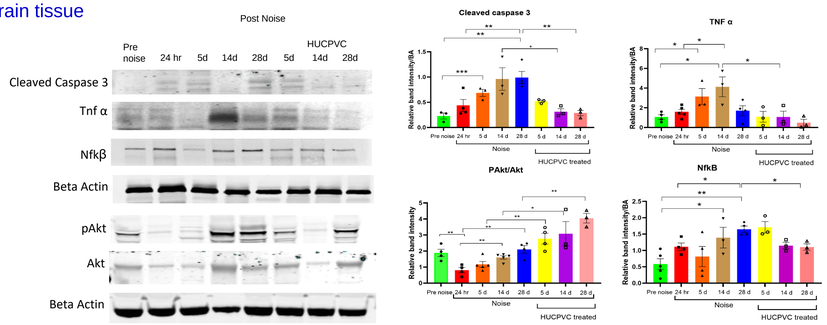


Fig 7. Western blot analysis to examine the effect of systemic injection of HUCPVC cells on apoptotic and inflammatory protein levels in the brain of noise-exposed rats. Bar diagrams represent the mean ± SEM level of the proteins. Beta-actin was used as a loading control. ,*p<0.05, **p<0.005, ***p<0.0005 , N≥3 per group.

Summary and Conclusion

- Significantly increased levels of inflammatory and apoptotic proteins (Tnf-α, cleaved-caspase 3, and NFkβ) in the brain tissue of noise-exposed rats. These increased levels were reversed in HUCPVC-treated groups.
- Noise exposure caused a decrease in the level of BDNF, and an increase in the level of inflammatory genes in the brain and cochlea tissue, and these changes were reversed in the HUCPVC-treated group

Conclusion: These findings show the protective effect of HUCPVC against noise-induced inflammation in the brain and cochlea.

References

1. Frye MD, et al. J Acoust Soc Am. 2019,146(5):4020.
2. Wang Q, et al. Front Genet. 2020, 28;11:968
3. Dhukhwa A, et al. Front Cell Neurosci. 2019, 3;13:444.
4. Tan WJ, et al. Histochem Cell Biol. 2016,146(2):219-30.

Acknowledgement

The authors thank the UHN animal care facility team for their excellent technical assistance.

CReATe Fertility Centre

Obstetrics & Gynaecology UNIVERSITY OF TORONTO

WCA World Congress of Audiology 19-22 September 2024 Paris, France CNIT Paris La Défense