

BIOLOGICAL BASES OF NOISE INDUCED HEARING LOSS (NIHL)

D. Henderson, Ph.D. and E. Bielefeld

Center for Hearing & Deafness, State University of New York at Buffalo,
215 Parker Hall, 3435 Main Street, Buffalo, NY 14214 USA

Tel: (716) 829-2001; Fax: (716) 829-2980; E-mail: donaldhe@acsu.buffalo.edu

Introduction Current noise standards in the United States are thirty years old and professionals in the field have confidence that a well-managed hearing conservation program is effective in preventing and controlling hearing loss in workers. In spite of what might seem to be a “solved problem”, there continues to be active research on the biological bases of NIHL. There is optimism about the new research because we are now beginning to understand some of the persistent remaining questions about NIHL. For example, studies of the cochlear efferent system may lead to an eventual test for susceptibility; studies of cochlear blood flow and control, reveal the importance of stable blood supply for resistance to noise and perhaps most importantly, new research on cell death in the cochlea has provided key insights into how the ear can be protected pharmacologically.

Cochlear efferent system(s?) The olivary cochlear bundle (OCB) efferent system can be divided into the medial olivary system (MSO) with cell bodies primarily in the contralateral medial superior olivary nucleus and highly branched synapse on the outer hair cells (OHC) and the lateral system (LSO) with cell bodies in the ipsilateral superior olivary nucleus and synapses on the dendrites of the VIII nerve under the inner hair cells (IHC). Papers by Rajan and Johnstone (1983), Rajan (1988) and Reiter and Liberman (1995) show that stimulation of the medial system provides a measure of protection from temporary threshold shift (TTS). Recently there has been a series of papers that have suggested a protective role for the LSO. Experiments by Zheng et al. (1999) and Liberman and Guo (1995), show that sectioning of the LSO pathway reduces spontaneous activity in the VIII nerve fibers but increases the dynamic range and maximum rate of the VIII nerve fibers.

Chinchillas and guinea pigs who are exposed to noise and have sectioned OCB (both LSO and MSO) develop greater amounts of PTS than control animals. Interestingly, if the OCB is only partially sectioned, there is no change in susceptibility. Presumably, the OCB is sufficiently redundant to operate without a full complement of nerve fibers.

Maison and Liberman (2000) have recently suggested that the degree of efferent suppression is a predictor or indicator of susceptibility to NIHL. In their experiment, efferent suppression was measured by contralateral stimulation during the measurement of DPOAE and then subjects were exposed to traumatic noise. Subjects with the largest suppression had the least NIHL, which is consistent with the idea that the efferent system modulates cochlear response to stimulation. However, there is some question about this conclusion. First, suppression of DPOAE is a small event and ranges from a fraction of a dB to 2 dB, but the variability with noise exposures can be extreme with a single exposure producing a range of 30 to 50 dB. Thus, it is difficult to reconcile the operating range of the efferent system with the variability of NIHL. Perhaps, if the other efferent system, the acoustic reflex co-varies in effectiveness with the OCB, then an individual's resistance to noise is partially determined by the transmitted sound as modulated by the acoustic reflex and the cochlear stimulation as modulated by the OCB.

Cochlear blood flow There have been many studies of changes on cochlear blood flow with exposure to noise (Perlman and Kimura, 1962; Prazma et al., 1987; Thorne and Nuttall, 1987; Quirk et al., 1992; Lamm and Arnold, 2000). Unfortunately, the data do not describe a consistent picture. Some studies have shown decreases in cochlear blood flow during or after noise, while others have shown increases. In the last few years, there have been several studies of surgical manipulation of the autonomic control of cochlea blood flow. Sectioning of the superior cervical ganglion (which can reduce cochlear blood flow when stimulated (Ren et al., 1993)) led to guinea pigs developing less TTS (Hildesheimer et al., 1991; Horner et al., 2001) and PTS (Hildesheimer et al., 2002). The stellate ganglion has a stronger influence on cochlear blood flow than does the superior cervical ganglion (Laurikainen et al., 1997), but has not been studied in relation to noise because blockade or section of the stellate ganglion is extremely difficult and must be done bilaterally. The alternative is to use adrenergic receptor antagonists as a means of piecing out the influence of the stellate ganglion on noise susceptibility. Studies have shown adrenergic blockers can increase cochlear blood flow (Ohlsén et al., 1991) and reduce susceptibility to noise (Hildesheimer et al., 1990). Further study is needed to determine the relative contribution of the stellate and superior cervical ganglia to individual noise susceptibility, and to determine if cochlear blood flow changes are the mechanism through which the autonomic fibers exert their influence on noise.

It is too early to consider manipulation of cochlea blood flow as part of a protective strategy for traumatic noise. The results do, however, reinforce the idea that changes in cochlea blood flow disturb the oxidative stress balance in the cochlea. Sectioning of the SCG may prevent or reduce ischemia caused by high levels of stimulation and reduce the generation of toxic free radicals.

Cell death We have known for years that hair cells continue to die for weeks after a traumatic noise exposure (Bohne, 1976; Hamernik et al., 1984). Recently, the pathway of cell death has been re-examined using an *in vivo* fixation approach. Hu et al. (2002) reported that immediately after a noise exposure (either a 4 kHz OB @ 105 dB x 2 hours or 155 dB impulse x 100 repetitions) there was a small lesion of OHC (<1 mm). Most of the nuclei surrounding the focal lesion are constricted or shrunken – a condition associated with apoptotic cell death. There are, however, a few OHC nuclei that are swollen – a condition associated with necrotic cell death. If the cochlea is stained for caspase 3 (an enzyme associated with terminal stages of apoptosis), the shrunken nuclei express caspase 3, while the swollen nuclei do not. The caspase staining confirms the pattern of apoptosis and necrosis.

If cochleas are examined at 2 days post-exposure, several interesting trends emerge. First, the size of the lesion (missing cells) increases substantially. Second, the apical or low-frequency margin of the lesion is relatively stable (i.e., a few missing OHC, but no transition cells), but the basal margin of the lesion still is highly active with cells beginning apoptosis.

Collectively, these results show that following a noise exposure, the cochlear lesion continues to expand, the expansion is based on prolonged apoptotic activity and the direction of the expansion is towards the base (probably because of the lower antioxidant concentration in base, Sha et al., 2001). The prolonged period of cell death may present an opportunity to intervene and reduce the eventual number of sensory cell death.

A rationale protection strategy requires that there is an understanding of the triggers and pathways of cell death. Several investigators, (Seidman et al., 1993; Liu, 1992; Ohelmiller et al., 1999; and Yamane et al., 1995) have provided evidence that high-level noise leads to an increase in reactive oxygen species (ROS) in the ear. Direct evidence of free radical formation following a traumatic noise exposure, was provided by Nicotera et al. (1999). They report that immediately after a noise exposure there is an orderly accumulation of ROS reaction products at the region of the OHC. Several days later, there is still evidence of ROS activity. The

Nicotera et al. (1999) result raises the issue of whether the ROS formation is the cause of the hair cell loss or the product of the hair cell loss. A partial answer to this question is provided by studies with paraquat, a chemical that reacts with molecular oxygen to produce the superoxide radical (O_2^-). When chinchillas are treated with PQ to the round window, there is a pathological process that superficially resembles noise-induced pathology (i.e., loss of OHC, general sparing of IHC and other cochlear tissue) (Bielefeld et al., 2003). The PQ results strongly implicate ROS as a cause of hair cell loss, thus it is reasonable to ask if strengthening the ear's antioxidant system protects it from noise damage.

Several studies have applied antioxidants, R-N6-phenylisopropyladenosine (R-PIA) or glutathione monoethyl ester (GEE), to the round window before a noise exposure and found that the subjects were protected from continuous noise (Hu et al., 1997) or impulse noise (Hight et al., 1999). The results are quite dramatic and show a substantial reduction in permanent threshold shift (PTS) and hair cell loss. Protection with the application of antioxidants to the round window is interesting in that it helps us understand the pathological process, but round window applications are not clinically possible. Kopke et al. (2000) has recently reported that systemic treatment with the antioxidant *N*-acetyl-L-cysteine (L-NAC), provided substantial protection from both continuous and impulse noise. These results are important because they show that systemic antioxidant treatment is effective in the sequestered spaces of the cochlea. The next challenge is to develop an orally delivered antioxidant with a practical level of bioavailability.

References

- Bielefeld, E., Zheng, X.Y., Hu, B., Carney, K., Nicotera, T., and Henderson, D. (2003) Threshold shift induced by paraquat-generated superoxide radicals. Abstract presentation at the Association for Research in Otolaryngology Mid-Winter Meeting; Daytona Beach, Florida; February 23-27, 2003.
- Bohne, B.A. (1976) Mechanisms of Noise Damage in the Inner Ear. In: Effects of Noise on Hearing. Henderson, D., Hamernick, R.P., Dosangh, D.S. and Mills, J.H. (Eds), Raven Press, N.Y. pp. 41-70.
- Hamernik, R. P., Turrentine, G., Roberto, M., Salvi, R., and Henderson, D. (1984) Anatomical correlates of impulse noise-induced mechanical damage in the cochlea. *Hearing Research*, 13, 229-47.
- Hight, N.G., Henderson, D., McFadden, S.L., Zheng, X.Y., and Ding, D.L. (1999) The effect of glutathione monoethyl ester (GSHee) on hearing loss and hair cell loss in chinchillas exposed to impulse noise. Assoc. for Research in Otolaryngology, St. Petersburg Beach, FL.
- Hildesheimer, M., Henkin, Y., Pye, A., Heded, S., Sahartov, E., Shabtai, E., and Muchnik, C. (2002) Bilateral superior cervical sympathectomy and noise-induced, permanent threshold shift in guinea pigs. *Hearing Research*, 163, 46-52.
- Hildesheimer, M., Sharon, R., Muchnik, C., Sahartov, E., and Rubinstein, M. (1991) The effect of bilateral sympathectomy on noise induced temporary threshold shift. *Hearing Research*, 51, 49-54.
- Hildesheimer, M., Muchnik, C., and Rubinstein, M. (1990) Iontophoresis with an adrenergic alpha-blocker in acoustic overstimulation. *Euro Arch of Oto-Rhino-Laryngol*, 247, 345-347.
- Horner, K., Giraudet, F., Lucciano, M., and Cazals, Y. (2001) Sympathectomy improves the ear's resistance to acoustic trauma-could stress render the ear more sensitive? *Euro J of Neurosci*, 13, 405-408.
- Hu, B.H., Henderson, D., and Nicotera, T. (2002) Involvement of apoptosis in progression of cochlear lesion following exposure to intense noise. *Hearing Research*, 166, 62-71.
- Hu, B.H., Zheng, X.Y., McFadden, S.L., Kopke, R.D., and Henderson, D. (1997) R-phenylisopropyladenosine attenuates noise-induced hearing loss in the chinchilla. *Hearing Research*, 113, 198-206.
- Kopke, R. D., Weisskopf, P. A., Boone, J. L., Jackson, R. L., Wester, D. C., Hoffer, M. E., Lambert, D. C., Charon, C. C., Ding, D., and McBride, D. (2000) Reduction of noise-induced hearing loss using L-NAC and salicylate in the chinchilla. *Hearing Research*, 149, 138-146.

- Lamm, K. and Arnold, W. (2000) The effect of blood flow promoting drugs on cochlear blood flow, perilymphatic pO₂ and auditory function in the normal and noise-damaged hypoxic and ischemic guinea pig inner ear. *Hearing Research*, 141, 199-219.
- Laurikainen, E.A., Ren, T., Miller, J.M., Nuttall, A.L., and Quirk, W.S. (1997) The tonic sympathetic input to the cochlear vasculature in guinea pig. *Hearing Research*, 105, 141-145.
- Liberman, M.C. and Gao, W.Y. (1995) Chronic cochlear de-efferentation and susceptibility to permanent acoustic injury. *Hearing Research*, 90, 158-168.
- Liu, E. (1992). Experimental study on the mechanism of free radicals in blast trauma-induced hearing loss. *Chinese J Otorhinolaryngol*, 27, 24-26.
- Maison, S. and Liberman, M. (2000) Predicting vulnerability to acoustic injury with a noninvasive assay of olivocochlear reflex strength. *J of Neurosci*, 20(12), 4701-4707.
- Nicotera, T., Henderson, D., Zheng, X., Ding, D., and McFadden, S. (1999) Reactive oxygen species, apoptosis and necrosis in noise-exposed cochleas of chinchillas. Abstract presentation at the Association for Research in Otolaryngology Mid-Winter Meeting, St. Petersburg, Florida. Abstract number 626.
- Ohlemiller, K. K., Wright, J. S., and Dugan, L. L. (1999) Early elevation of cochlear reactive oxygen species following noise exposure. *Audiol Neurotol*, 4, 229-36.
- Ohlsén, K., Baldwin, D., Nuttall, A., and Miller, J. (1991) Influence of topically applied adrenergic agents on cochlear blood flow. *Circulation Res*, 69, 509-518.
- Perlman, H. and Kimura, R. (1962) Cochlear blood flow in acoustic trauma. *Acta Otolaryngol*, 54, 99-110.
- Prazma, M., Vance, S., Bolster, E., Pillsbury, H., Duncan, M., and Postma, M. (1987) Cochlear blood flow: the effect of noise at 60 minutes' exposure. *Arch of Otolaryngol Head Neck Surg*, 113, 36-39.
- Quirk, W., Avinash, G., Nuttall, A., and Miller, J. (1992) The influence of loud sound on red blood cell velocity and blood vessel diameter in the cochlea. *Hearing Research*, 63, 102-107.
- Rajan, R. and Johnstone B.M. (1983) Crossed cochlear influences on monaural temporary threshold shifts. *Hearing Research*, 9, 279-94
- Rajan, R. (1988) Effect of electrical stimulation of the crossed olivocochlear bundle on temporary threshold shifts in auditory sensitivity. I. Dependence on electrical stimulation parameters. *J Neurophysiol* 60, 549-568.
- Reiter, E. and Liberman, M.C. (1995) Efferent-mediated protection from acoustic overexposure: relation to slow effects of olivocochlear stimulation. *J Neurophysiol*, 73, 506-514.
- Ren, T., Laurikainen, E.A., Quirk, W.S., Miller, J.M., and Nuttall A.L. (1993) Effects of electrical stimulation of the superior cervical ganglion on cochlear blood flow in guinea pig. *Acta Otolaryngol*, 113, 146-151.
- Seidman, M.D., Shivapuja, B.G., and Quirk, W.S. (1993) The protective effects of allopurinol and superoxide dismutase on noise-induced temporary threshold shifts. *Otolaryngol. Head Neck Surg*. 109: 1052-1056.
- Sha, S.H., Taylor, R., Forge, A. and, Schacht, J. (2001) Differential vulnerability of basal and apical hair cells is based on intrinsic susceptibility to free radicals. *Hearing Research*, 155, 1-8.
- Thorne, P. and Nuttall, A. (1987) Laser Doppler measurement of cochlear blood flow during loud sound exposure in the guinea pig. *Hearing Research*, 27, 1-10.
- Yamane, H., Nakai, Y., Takayama, M., Konishi, K., Kagawa, T., Shibata, S., Kato, A., Sunamisk, J. and, Kawakatsa, C. (1995) The emergence of free radicals after trauma and strial blood flow. *Acta Otolaryngol. Suppl.* 519, 87-92.
- Zheng, X.Y., Henderson, D., McFadden, S., Ding, D., and Salvi, R. (1999) Auditory nerve fiber responses following chronic cochlear de-efferentation. *The Journal of Comparative Neurology*, 406, 72-86.