709 D-Methionine (D-Met) Rescue From Noise-Induced Hearing Loss: Post-Administration Intervals

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D-met protects against cisplatin-induced, aminoglycoside-induced and noise-induced hearing loss. However, many noise exposures cannot be fully anticipated in advance (ie .military and emergency personnel). Therefore an otoprotective agent that could be administered after the noise exposure and still prevent permanent noise induced hearing loss (NIHL) would have great clinical applicability. Because the otoprotective/rescue agent may not be immediately available to someone suddenly exposed to noise, it is of clinical interest to determine how long after the noise exposure D-met can be administered and still protect against NIHL.

In this study, 5 groups of male chinchillas Laniger were individually exposed to a 105 dB SPL narrow band of noise centered at 4 kHz for 6 hours. In the 4 experimental groups, D-met (200 mg/kg per dose) was initially administered at 1, 3, 5 or 7 hours hour post noise exposure plus 4 additional doses BID (5 doses) at 12 hour intervals. The control group received equivalent volume saline injections.

Auditory brainstem response testing (ABR) was performed just prior to the noise exposure and again on post-exposure days 1, 14 and 21. ABR thresholds were measured in response to tone bursts centered at the frequencies of 2, 4, 6, and 8 kHz. An intensity series was obtained for each animal from 100 to 0 dB peak sound pressure level (SPL) for tone bursts in 10 dB decrements. Threshold was defined as the lowest intensity capable of eliciting a replicable, visually detectable response.

Data collection is ongoing. Based on results to date, at 21 days after the noise exposure

D-met significantly reduced noise-induced ABR threshold shifts when administered starting at 1, 3 or 5 hours after the cessation of the 6 hour noise exposure. At the time of abstract submission, we have data on only 3 animals at the 7 hour post administration interval which appears to reduce the ABR threshold shift but has not yet reached significance.

710 Cochlear Injuries After Exposure to a Kurtotic Noise and Styrene and Its Protection

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Combined exposure to both noise and aromatic solvents such as styrene is common in many industries. In this study, cochlear electrical responses and injuries of auditory hair cells as well as supporting cells (including cell death) were determined in rats after exposure to a high kurtotic noise and styrene. Protection against the cochlear injuries by antioxidants (N-Acetyl-L-cysteine and idebenone) was also investigated.

The noise exposure (10-20 kHz, at a level of 100 dB SPL with 110-dB impact noise [40-ms duration, 1-ms rise and 30 ms fall time, 1/s], 6 hrs per day for 5 days a week for 3 weeks) induced a frequency-dependent permanent threshold shift (PTS) with a maximal level of about 30 dB at 12 kHz. Morphologic examination in some individuals with severe functional loss showed no sign of damage to auditory hair cells (stereocilia) or supporting cells. The styrene exposure attacked Deiter¡¯s cells first. For a short-period styrene exposure (7 days, 1/d at a dosage of 800 mg/kg by gavage), the majority of Deiter¡¯s cells in the middle turn showed condensed nuclei, but the outer hair cells (OHCs) looked normal. The 3-week styrene exposure (at 400 mg/kg) destroyed almost all of the 3rd row OHCs and some in the 2nd and 1st rows in the middle turn. Surprisingly, there was only a slight PTS (<5 dB) observed at middle frequencies. The combined exposure showed potentiative effect in the middle frequency region where both the noise and styrene showed toxic effects, functionally or structurally. Treatment with N-acetyl-L-cysteine and idebenone significantly protected against the functional loss induced by the noise and styrene.

The results indicate that styrene exposure may cause a severe cochlear injury before a hearing loss can be detected. Risk of noise exposure may be significantly increased in the styrene-exposed individuals. The cochlear damage can be partially protected with application of antioxidants.

This study was supported by NIOSH grant 1R01OH008113-01A1.

711 Free Radical Scavengers, Vitamins A, C, and E, Plus Magnesium Reduces Noise Trauma

Colleen Le Prell[1], Larry Hughes[2], Josef Miller[1]

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Free radical formation in the cochlea plays a key role in the development of noise-induced hearing loss (NIHL). The amount, distribution, and time course of free radical formation have been defined, including a clinically significant formation of both reactive oxygen species and reactive nitrogen species 7-10 days following noise exposure. Noise-induced reduction in cochlear blood flow, now known to reflect free radical formation, has also been described. Here we report that the antioxidant agents, vitamins A, C, and E, act in synergy with magnesium to effectively prevent noise-induced trauma in the guinea pig. Neither the antioxidant agents nor magnesium reliably reduced NIHL or sensory cell death when these agents were delivered alone, at the doses we used. In combination, however, they were highly effective in reducing both hearing loss and cell death. The preventions of noise-induced trauma was clinically significant, and statistically reliable, even with treatment initiated just one hour prior to noise exposure. This study supports roles for both free radical formation and noise-induced vasoconstriction in the onset and progression of NIHL. Identification of this safe and effective antioxidant intervention that attenuates NIHL provides a compelling

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CONFERENCE OBJECTIVES

After attending the Scientific Meeting participants should be better able to:

1. Understand current concepts of the function of normal and diseased ears and other head and neck structures.
2. Understand current controversies in research methods and findings that bear on this understanding.
3. Understand what are considered to be the key research questions and promising areas of research in otolaryngology.

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President's Message

Welcome to the mile high city of Denver, Colorado for the 30th Annual MidWinter Meeting of the Association for Research in Otolaryngology. This is the first time we've been landlocked for the February meeting; we've moved from the west coast to the east coast of Florida, from the Mississippi delta to Chesapeake Bay. Hopefully, Denver won't be as cold as Baltimore was last year. Denver is a pleasant city with easy access to winter sports activities (hopefully, snowboarding and ski-lodge related injuries will be minimal). The Hyatt Hotel is an excellent facility: it is less that one year old with terrific meeting space and great views of the city and mountains. Be sure to visit the many shops and restaurants in the LODO district (LOwer DOwntown) and Larimer Square, as well as the new, Daniel Libeskind designed wing of the Denver Art Museum, all within walking distance of the hotel.

Thanks to the good response from our members, we have scheduled many interesting and innovative symposia, including: Neurobiology of Vocal Communication: Beyond Acoustic Features, Specification of the Auditory and Vestibular Hindbrain, Wnt Signaling Pathways and Inner Ear Development, Spatial and Binaural Hearing: Perception and Physiology, Beyond Cochlear Implants: Functional Stimulation and Recording in the Auditory Nervous System, and Ion Transport in the Stria Vascularis: Modeling and Experiment. The short course presented Saturday evening will be Translational Research in Otolaryngology. The presidential symposium on Sunday morning is titled: Ear and Brain: Hearing beyond the Cochlea.

The ARO continues to search for a new meeting venue that will maintain the excellent scientific and social experience of meetings past. Under the constraints of the present economy, the ARO Council and Management Team are working hard to find affordable venues in attractive locations. You may not be aware of the behind-the-scene efforts needed to arrange the MidWinter meeting and run the organization, but thanks are certainly due to the ARO council and to the Talley Management Group for their excellent work in organizing the Denver meeting. In particular, we applaud the hard work of John Middlebrooks (serving double duty as Council member and Program Organizing Committee Chair) and Lisa Astorga (Meeting Coordinator).

This year we have been able to continue to offer travel awards to research trainees, thanks to generous donations from the AAO, DRF, and AAA/AAAF. These funds allow for an important function of the MidWinter meeting: introducing young people to the network of scientists and researchers of the ARO. Young researchers are vital to the health of the organization, as "new blood" invigorates both the scientific and social interactions made possible by the meeting. I vividly remember (well, maybe not vividly) my first scientific meeting and the impact it had on my career (of which the

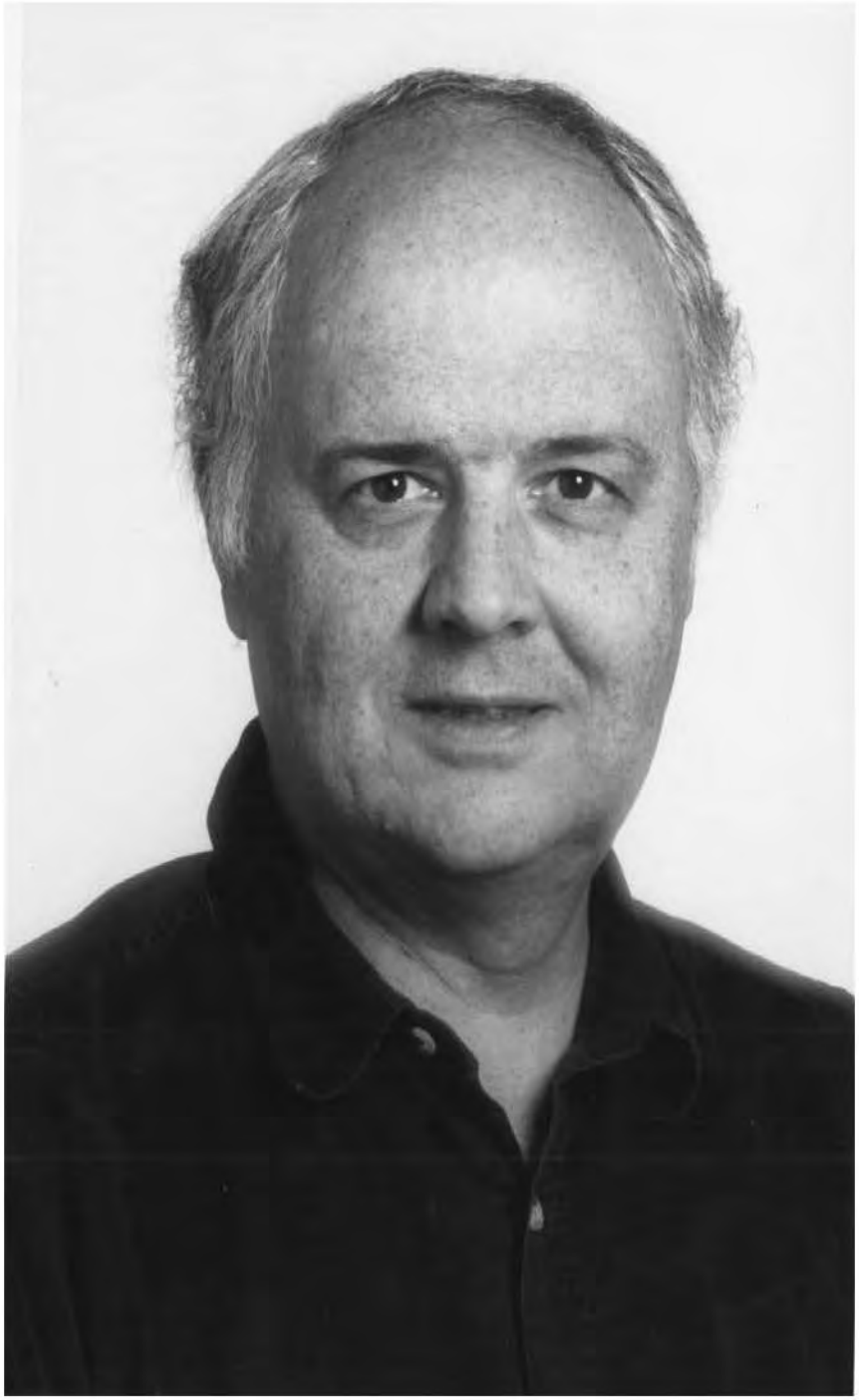
tequila-fueled barn-burners were no small part). We welcome all new attendees and look forward to their ongoing participation in the ARO.

Speaking of “young” researchers, Eric Young has been selected to receive the Award of Merit this year. The title of Eric's Presidential Lecture will be Circuits and Signal Representations in the Auditory System. Many former students and colleagues will participate in this tribute to Eric and his great influence on auditory neuroscience.

Ruth Anne Eatock has assumed editorship of the JARO, while simultaneously moving to a new institution (she is now at the Eaton-Peabody laboratory and the Department of Otology and Laryngology, Harvard Medical School). Anyone who has ever relocated their research lab knows the extra effort required to establish yourself in a new institution. The fact that Ruth Anne has also taken on the JARO editorship deserves our admiration for her commitment to public service.

I expect we will have another fun and productive MidWinter meeting. Attendance and membership in the ARO has remained strong over recent years, despite the difficulties associated with venue changes. The number of registrants and submitted abstracts has been stable over the last 5 years. As the MidWinter Meeting moves to new locations in the future, members remain strongly committed to the meeting and to the organization. It's clear that the ARO is much more than an organization - it’s a true community of science. I feel fortunate and look forward to “brainstorming” with colleagues, meeting new people, and relaxing with old friends in Denver.

Bob Shannon



Eric D. Young, PhD

2007 Award of Merit Recipient

Eric D. Young, PhD
2006 Recipient of the Award of Merit

The 2007 Award of Merit will be given to Eric D. Young in recognition of his many seminal contributions to our understanding of how the brain enables us to perceive sounds. In many ways Eric's approach to research has set the standard for hearing research throughout the world. Educated with extraordinary depth in engineering, computation and biology, Eric has time and again demonstrated the value of truly integrated experimental and theoretical studies of the nervous system. Eric possesses an unusually independent spirit. He has never hesitated to venture into new territory, whether to adopt new experimental paradigms or cutting edge theoretical constructs.

The source of this independence is undoubtedly to be found in Eric's youth on his family ranch, the Bar-L in Elko, Nevada. By the time he was 12, he was driving hay-cutting machinery as his summer vacation activity. However, early on Eric knew that he was not meant to be a cattle rancher and by the time he reached high school had discovered what would become a life-long passion – building and programming computers. The computer skills he developed at an early age have made him a world leader in innovative neurophysiological data gathering and analysis. Eric left the ranch to study engineering at Caltech where he received his BS in 1967. Having met and married Pamela Perkins, Eric ventured to the East Coast where he earned his PhD in Biomedical Engineering from Johns Hopkins in 1972. His thesis, "Recovery from Sound Exposure—A Comparison of Psychophysics and Physiology" was the first study in what would become one theme in Eric's research career, namely model-driven explorations of the relationship between auditory-nerve discharge patterns and psychophysical performance. Eric's postdoctoral fellowship took him to Jay Goldberg's lab at the University of Chicago in 1972, where he launched his second major research thrust: to understand the function of the dorsal cochlear nucleus. Johns Hopkins was fortunate to be able to convince Eric to return to Baltimore in 1975. He is currently Professor of Biomedical Engineering, Neuroscience and Otolaryngology/Head and Neck Surgery.

Since his postdoctoral days, Eric has led an effort to understand the role of the dorsal cochlear nucleus (DCN) in hearing; he and his colleagues have made a strong case that one of the roles of the DCN is to enable mammals to use spectral cues to localize sound sources. Elegant, direct experimental approaches together with rigorous analyses yield answers to a beautifully logical series of questions. It is revealing to review how the findings unfolded over the past thirty years, both for what has been learned about the DCN and for what it reflects about how a very fine scientist formulated a logical series of questions and developed approaches to address them.

Eric's first paper about the DCN was published in 1976 with Bill Brownell, describing his postdoctoral work. The immediate impetus was a 1973 paper by

Ted Evans and Phil Nelson, who found that anesthesia greatly altered the properties of neurons in the DCN. Accordingly, Eric and Bill decided to work in decerebrate cats. Probing single unit responses with tones and noise revealed consistent patterns. While type II/III units responded with excitation to tones and were unresponsive to broadband noise, type IV units were excited only at low levels and responded vigorously to noise.

The work continued after Eric returned to Hopkins. Which were the cells that produced these responses? He and his colleagues demonstrated that type IV units were principal cells because their axons could be stimulated from the output pathway of the DCN; some type II/III units (now called type II) could be driven antidromically from the ventral cochlear nucleus (VCN) but none could ever be driven by stimulation of the dorsal acoustic stria indicating that they were local neurons. Are these two neuronal types synaptically connected? Herb Voigt and Eric recorded from pairs of neurons in the DCN. The reciprocal response areas together with cross-correlation analysis left no doubt that type II units inhibit type IV units. What is the source of the inhibition that prevents type II units from responding to broadband noise? This question was addressed first by Bill Shofner and Young and revisited by Israel Nelken and Eric; broadly tuned inhibitory neurons in the VCN shape responses to broadband noise. By the 1990s, Eric and his postdoctoral colleagues, George Spirou, Kevin Davis, and Eli Nelken were able to account for all features of the responses of type II and type IV units to sound on the basis of their inputs.

Papers with George Spirou and Lina Reiss showed with startling clarity that type IV units are beautifully suited for encoding the presence of spectral notches, important spectral cues for localizing sounds. Eric recognized that responding to sounds is only a part of the DCN's job, reflecting only the processing carried out in the deep layer of the DCN. A separate system of inputs comes to the DCN through the granule cells in the superficial layer. Granule cells receive input from widespread regions of the brain, including a prominent input from the dorsal column nuclei. How do the dorsal column nuclei influence the principal cells of the DCN? Eric and his colleagues once again approached the question directly. Shocks to the dorsal column nuclei strongly inhibited type IV units. With Biomedical Engineering graduate student Patrick Kanold Eric showed that much of the somatosensory information to the DCN reflects proprioceptive information about the pinna. These findings were attractive because information about the position of the pinna has to be taken into account for interpreting spectral cues. Eric's most recent work with Steve Chase addresses the question how information from the DCN is used at the next stage of the auditory pathway, the inferior colliculus.

While pursuing studies of the DCN, Eric managed also to devote a major effort aimed at understanding the relationship between stimulus encoding in the auditory nerve and human perception of complex stimuli like speech. This work first appeared in 1979 in two papers with one of the authors of this citation (MBS)

which demonstrated the power of the population method in which the responses to a stimulus are recorded from a large number of neurons and from these the responses of the whole auditory nerve are inferred. In a tour de force of data analysis, Eric showed how the spectrum of a speech stimulus might be represented in the detailed temporal patterns of auditory nerve discharges. For the past 25 years Eric and his colleagues have continued to detail the auditory nerve encoding of speech in a wide range of circumstances, including background noise and inner ear acoustic trauma. The results of these studies include the need for a reexamination of commonly held ideas about the neural correlates of loudness recruitment and suggestions for the design of new hearing aids based on models for signal processing in the impaired cochlea.

Eric's work is exceptional. In answering a logical series of questions, he has revealed much about how the auditory system works. His papers are a pleasure to read not only for their conclusions but because each is documented meticulously, and analyzed rigorously with sophisticated techniques. His papers are also exceptional in their scholarship. We cannot recall ever thinking that a relevant reference had been omitted. The rigor extends to the way conclusions are drawn in Eric's papers. It was only in the 1990s that his papers began to suggest that the DCN might play a role in making use of spectral cues. Even then, the suggestion served more to provide a framework than to inflate the significance of the work.

Eric is a superb teacher and mentor. For five years he directed the Hopkins Biomedical Engineering graduate Program and has been one of the most active and successful teachers in the Department of Biomedical Engineering. He has been a mentor to a generation of graduate students and postdoctoral fellows who have gone on to successful careers in auditory neuroscience, including Herb Voigt, John White, Kevin Franck, Patrick Kanold, Lina Reiss, Steve Chase, Bill Shofner, George Spirou, Israel Nelken, Roger Miller, Kevin Davis, Ian Bruce, and Michael Heinz.

Eric is also exceptional as a colleague and as an understated but authoritative scientific leader. At meetings it is a pleasure to see his tall frame rise from a seat or appear at a poster to ask a question. Those questions are penetrating, but not aggressive or personal, and they address central issues. They are questions one does not ignore.

For all of his exceptional contributions, Eric Young richly deserves the ARO Award of Merit. On behalf of his many friends and colleagues it is our privilege to congratulate him on this special recognition.

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