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Efficacy of the Antioxidant N-acetylcysteine (NAC) in Protecting Ears Exposed to Loud Music

Steven Kramer*
Laura Dreisbach*
Jill Lockwood†
Kristy Baldwin*
Richard Kopke‡
Shawn Scranton§
Michael O'Leary**

Abstract

Antioxidants have been reported to be effective in reducing acoustic trauma in animal models but have not been studied in humans. In this study, the antioxidant N-acetylcysteine (NAC) was evaluated to determine if it would reduce temporary changes in auditory function as a result of exposure to loud music in humans. Pure-tone thresholds and distortion product otoacoustic emissions (DPOAEs) were collected in 31 normal-hearing participants, using a randomized, double-blind, placebo-controlled design, before and after two hours of live music in a nightclub. Using repeated measures analysis of variance, no statistically significant differences were found between participants who received NAC versus a placebo for any of the outcome measures. Across all subjects, the largest pure-tone threshold shift occurred at 4 kHz. DPOAE measures were characterized by reductions in amplitude and a trend for shorter group delay values. When the 3 and 4 kHz data were examined by imposing specific criteria of greater than 2 dB DPOAE amplitude reductions and 10 dB or greater pure-tone threshold shifts, DPOAE reductions occurred more often at 3 kHz, and pure-tone shifts occurred more often at 4 kHz.

Key Words: Antioxidants, distortion product otoacoustic emissions, loud music, N-acetylcysteine, noise exposure, noise-induced hearing loss, socioacusis, temporary threshold shift

Abbreviations: DPOAEs = distortion product otoacoustic emissions; GSH = glutathione; NAC = N-acetylcysteine; PTS = permanent threshold shift; ROS = reactive oxygen species; TTS = temporary threshold shift

Sumario

Se ha reportado que los antioxidantes son efectivos en reducir el trauma acústico en modelos animales, pero ésto no han sido estudiados en humanos. En este estudio, se evaluó el antioxidante N-acetilcisteína (NAC) para determinar si podría reducir los cambios temporales en la función auditiva, como consecuencia de la exposición en humanos a música de alta intensidad. Se registraron

*San Diego State University, School of Speech, Language, and Hearing Sciences, San Diego, CA; †Providence Speech and Hearing Center, Orange, CA; ‡Hough Ear Institute, Oklahoma University Health Science Center, Oklahoma City, OK; §Salmedix Inc., San Diego, CA; **Senta Medical Clinic, San Diego, CA

Steven J. Kramer, School of Speech, Language, and Hearing Sciences, San Diego State University, 5500 Campanile Dr., San Diego, CA 92182-1518; Phone: 619-594-6140; Fax: 619-594-7109; E-mail: skramer@mail.sdsu.edu

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umbrales para tonos puros y emisiones otoacústicas por productos de distorsión (DPOAE) en 31 participantes con audición normal, utilizando un diseño aleatorio, doble ciego, controlado por placebo, dos horas antes y después de la exposición a música en vivo en un club nocturno. Usando análisis de variancia de medidas repetidas, no se encontraron diferencias estadísticamente significativas entre los participantes que recibieron NAC versus placebo, en ninguna de las medidas de resultado. En todos los sujetos, el cambio de umbral tonal más grande ocurrió a 4 kHz. Las DPOAE mostraron reducciones en la amplitud y una tendencia a valores más cortos en retraso grupal. Cuando se examinaron las frecuencias de 3 y 4 KHz, imponiendo criterios específicos de reducción de más de 2 dB en la amplitud de las DPOAE y 10 dB o más en el cambio del umbral tonal, la reducción en las DPOAE ocurrió más a menudo en 3 kHz y los cambios tonales ocurrieron más a menudo en 4 kHz.

Palabras Clave: Antioxidantes, emisiones otoacústicas por productos de distorsión, música de alta intensidad, N-acetilcisteína, exposición a ruido, hipoacusia inducida por el ruido, socioacusia, cambio temporal del umbral

Abreviaturas: DPOAE = emisiones otoacústicas por productos de distorsión; GSH = glutatión; NAC = N-acetilcisteína; PTS = cambio permanente de umbral; ROS = especies reactivas al oxígeno; TTS = cambio temporal de umbra

The general health benefits of antioxidants have been a topic of interest in the health conscious public for a number of years, and there are many commercially available antioxidant nutritional supplements, one of which is N-acetylcysteine (NAC). Under normal function, antioxidant defenses within the cells neutralize oxidants that are produced during routine metabolism, preventing their harmful effects (Freeman and Crapo, 1982; Clerici et al, 1995). There has been a growing interest in the use of antioxidants as a means of protecting the ear from noise exposure, based on animal studies that have demonstrated a reduction in permanent threshold shifts (PTS) and complicated results for temporary threshold shifts (TTS) with NAC in chinchillas and rats following excessive exposure to noise (Kopke et al, 2000; Ohinata et al, 2003; Duan et al, 2004).

The above-mentioned animal studies used relatively high doses (at least 325 mg/kg) of intraperitoneal injections of NAC and exposed the animals to long durations and high noise levels. However, NAC also has been reported to be effective in animals at dosages at least as low as 50 mg/kg (Kopke et al, 2004). At this time it is not known what dosage level of NAC would be appropriate for humans or whether it can be effective in preventing TTS. The present study was undertaken as an initial step to determine if commercially available NAC could provide some benefit in reducing temporary changes in auditory function in humans exposed to loud music in a nightclub setting. The efficacy of a single dose of NAC in reducing TTS from loud music was tested using a randomized, double-blind, placebo-controlled design. An additional purpose of this study was to document temporary changes in auditory function in a nightclub setting and compare results obtained with pure-tone threshold measures and distortion product otoacoustic emissions (DPOAEs).

Antioxidants and Hearing

Protection of cochlear hair cells from damage due to noise exposure is essential in order to prevent the onset of noise-induced hearing loss. For natural intrinsic protection, hair cells rely on antioxidant defenses, such as antioxidant enzymes, vitamins C and E, and glutathione (GSH) (Yamane et al, 1995; Ohlemiller and Dugan, 1999; Ohlemiller et al, 1999).

The use of pharmaceuticals as a means of protecting and/or repairing the ear has been an area of recent research (Hu et al, 1997; Fernandez-Checa et al, 1998; Yamasoba et al, 1998; Hu et al, 2000; Kopke et al, 2000, 2002; Ohinata et al, 2003; Pourbakht and Yamasoba, 2003; Duan et al, 2004). There is accumulating evidence in animal models, for example, chinchilla and rat, that hair cells undergo oxidative stress when exposed to excessive levels of noise (Gillissen et al, 1997; Kopke et al, 1999; Seidman et al, 2000). When

hair cells experience oxidative stress, reactive oxygen species (ROS) and free radicals are produced. When excessive amounts of ROS or free radicals are released, the natural intrinsic defenses can be overwhelmed, resulting in the reduction of GSH and possible cell injury or death (Kopke et al, 1999; Atlante et al, 2001). When GSH cellular levels are reduced, noise-induced damage to the cochlea intensifies and thresholds increase (Yamasoba et al, 1998; Ohinata et al, 2000). Increasing GSH or adding antioxidant compounds, in particular N-acetylcysteine (NAC), a known ROS scavenger and GSH precursor, can reduce the damage in hearing experienced after exposure to noise, generally demonstrated by less threshold shifts and less outer hair cell loss for those treated with NAC compared to nontreated controls (Hu et al, 1997; Fernandez-Checa et al, 1998; Hu et al, 2000; Kopke et al, 2000; Ohinata et al, 2003; Duan et al, 2004; Kopke et al, 2004). Administration of NAC may be more advantageous than GSH because NAC is not as readily metabolized and can be transported into more cell types (Meister, 1991). Zou et al (2004) demonstrated in animals that NAC was present in endolymph, perilymph, and cerebrospinal fluid up to six hours after oral administration.

To date, there is only one published abstract of a study in humans that examined the effectiveness of NAC on auditory function in participants exposed to loud music (Toppila et al, 2002). Participants were administered an oral dose of NAC (400 mg) or placebo prior to a four-hour exposure to loud music at a nightclub (average exposure level was 92–94 dBA). Average TTS after the exposure was 10 dB at 4 kHz; however, no significant differences were found between the NAC and placebo groups for pure-tone thresholds. Balance function, assessed with posturography, was reported to be significantly better in the NAC group.

The beneficial effects of NAC in preventing cell damage or death from noise exposure in animal models offers promise for using antioxidant agents as a protective therapy against noise-induced cochlear damage in humans. The potential role of NAC as a preventive measure for individuals who anticipate exposure to unsafe noise levels could have great benefit due to its over-the-counter accessibility as a nutritional supplement and favorable side effect profile (Miller and Rumack, 1983; De Rosa et al, 2000). Furthermore, NAC has been a safe and effective Federal Drug Administration (FDA) approved oral treatment for acetaminophen overdose for over 20 years.

Environmental Noise Exposure

Both PTS and TTS in hearing are well-documented consequences of excessive noise exposure and affect a large segment of society (Melnick, 1978, 1991; Mills 1982; National Institutes of Health [NIH], 1990; Ohlin, 1990; Brookhouser, 1994; Alberti, 1998; National Institute on Deafness and Other Communication Disorders [NIDCD], 1998; Suter, 2000). Generally, the effects of noise-induced hearing loss are evidenced by decreased hearing sensitivity in the 3–6 kHz range, with a characteristic notch at 4 kHz (Cooper and Owen, 1976; Quaranta et al, 1998). Threshold shifts arising from noise exposure are associated with changes in the mechanical and sensory structures of the cochlea (Liberman and Beil, 1979; Lim and Dunn, 1979; Bohne and Clark, 1982; Liberman et al, 1986; Nordmann et al, 2000). Although individuals will vary in their susceptibility, the risk of noise-induced TTS occurs at levels lower than those associated with PTS (Kryter et al, 1966; Melnick, 1976; Ward et al, 1976; Mills et al, 1979; Mills, 1982). The size of the TTS and the rate of recovery are affected by the duration and intensity of the noise exposure (Melnick, 1978). According to Mills (1982), an octave band of noise, centered in the midfrequency range and presented as low as 65–70 dB SPL, can cause a temporary hearing loss in humans.

Individuals are at risk of developing hearing loss through participation in recreational activities, such as those involving firearms, loud music, and engine noises (Davis et al, 1985; Clark, 1991; Suter, 1992; Axelsson, 1996; Meyer-Bisch, 1996; Hellstrom et al, 1998; Metternich and Brusis, 1999; Peters, 2003). These recreational noise exposures often exceed the occupational safety standards of 90 dBA as established by the Occupational Safety and Health Administration (OSHA; 1983) or 85 dBA as established by the National Institute for Occupational Safety and Health (NIOSH; 1998).

Smith et al (2000) found that almost 95%

of questionnaire respondents between 18 and 25 years of age attended nightclubs, where noise exposure levels were estimated to be between 85–105 dBA. Of this group, approximately 66% reported temporary effects on their hearing, including dullness of hearing and/or tinnitus. Liebel et al (1996) reported average sound levels in a nightclub of 105 dBA. Gunderson et al (1997) made sound level measurements for different staff members in nightclubs and found sound levels ranged from 94.9–106.7 dBA. Bray et al (2004) reported that disc jockeys in nightclubs were exposed to sound levels averaging 98–108 dBA. Seventy percent of the disc jockeys reported having experienced dullness in their hearing, and 74% reported having experienced tinnitus. Although a majority of the disc jockeys indicated concern for noise-induced damage to their hearing, only three of the disc jockeys reported use of hearing protectors during their work shift.

The purpose of the present study was to determine whether a single dose of NAC (900 mg), higher than the 400 mg dose used by Toppila et al (2002), could prevent temporary changes in auditory function in human participants following exposure to loud music. Changes in auditory function were documented using behavioral pure-tone thresholds and distortion product otoacoustic emissions (DPOAEs). DPOAE measures were included because they have been reported to be sensitive to the physiologic activity of the outer hair cells, which are vulnerable to injury (Kim, 1980; Kim et al, 1980; Lonsbury-Martin et al, 1987; Brown et al, 1989; Probst et al, 1991; Whitehead et al, 1992; Engdahl and Kemp, 1996; Liebel et al, 1996; Telischi et al, 1998; Katbamna et al, 1999; Namyslowski et al, 2004). DPOAE testing included frequency sweeps and calculations of group delay (slope of the phase versus frequency curve) to characterize cochlear function (e.g., Whitehead et al, 1996; Dreisbach and Siegel, 2001) because some investigators have suggested that DPOAE group delay could be a more sensitive indicator of cochlear damage than DPOAE amplitude measures (Telischi et al, 1998; Katbamna et al, 1999; Namyslowski et al, 2004). It was hypothesized that NAC would have a protective effect against temporary acoustic trauma, evidenced by less pure-tone threshold shift, less reduction in DPOAE amplitude, and less of a change in DPOAE group delay for those participants who took NAC compared to those who took a placebo. Comparisons were also made between pure-tone and DPOAE measures in documenting temporary changes in auditory function related to exposure to loud music.

METHODS

Participants

Eligible participants were screened in a sound-attenuating test suite on the university campus prior to the experimental sessions and were required to have pure-tone thresholds less than 25 dB HL at 1, 2, 3, 4, 6, and 8 kHz. Eligible participants also had to have DPOAEs with amplitudes greater than -20 dB SPL and 6 dB above the noise floor in at least four out of the six f_2 frequencies (2, 3, 4, 5, 6, and 8 kHz) tested. Thirty-two participants aged 19 to 29 years (mean 22 years), meeting the above criteria, were recruited for the experimental sessions. Participants were paid for their participation at the completion of the study. The study was approved by the Institutional Review Board at San Diego State University.

Selection of NAC Dosage Level

The NAC used in this study was a specially formulated 900 mg effervescent tablet. The 900 mg dosage level of NAC was chosen based on animal research demonstrating protective effects at dosage levels at least as low as 50 mg/kg (Kopke et al, 2004). A 50 mg/kg dose given to chinchillas would be about 8 mg/kg for humans with the assumption that animals metabolize drugs approximately six times faster than humans. Using an average weight for humans of 64 kg, the projected minimum effective NAC dosage would be 512 mg; thus, a 900 mg dosage would be about 1.75 times the minimum amount. The 900 mg dosage level of NAC is about 2.25 times the amount used by Toppila et al (2002), and is also consistent with the dosage level on commercially available NAC product labels.

Procedures

Pure-tone thresholds and DPOAEs were collected before and after two hours of live music in a nightclub. Using a randomized, double-blind design, half of the participants took NAC, and the other half of the participants took a placebo, identical in appearance and taste to the NAC tablet. The effervescent tablets were dissolved in eight ounces of water. The study was conducted on two nights at a nightclub hosting live music. The nightclub was open to patrons 18 years and older. The 32 eligible participants were asked to attend one of the two test nights at an assigned appointment time. Appointment times for each night of the study were established to allow four groups of four participants to be tested at 30-minute intervals. Each group was scheduled to arrive 90 minutes before entering the nightclub. Prior to participation, written informed consent was obtained from each participant. Participants were first administered a Breathalyzer test to ensure no alcohol was consumed prior to the study. Female participants took an FDA-approved, over-the-counter, urine human chorionic gonadotropin (hCG) detection test to screen for pregnancy. The Breathalyzer and pregnancy tests were administered by an experienced technician to one participant at a time in a commercial van located in the parking lot adjacent to the nightclub.

Pre-exposure pure-tone and DPOAE measures were obtained in a hearing conservation test van located in the parking lot adjacent to the nightclub. The test van had four separate test booths, approximately 2.5' X 5', which were in compliance with the maximum permissible ambient noise levels specified by the Hearing Conservation Amendment (OSHA, 1983). Two of the test booths were used to measure pure-tone thresholds, and the other two test booths were used to measure DPOAEs. The participant and tester were seated inside the test booth along with the test equipment. The testers who performed the pure-tone threshold measures were seated with portable audiometers placed on their laps. The equipment used to measure DPOAEs was set up on the bench inside each of the test booths. With these arrangements, all four participants in each group were tested at the same time. Two participants within a group were tested for pure-tone thresholds first, and the other two participants were tested for DPOAEs first. The order of testing was randomly assigned within each group.

Following the completion of pure-tone and DPOAE testing, the group of four participants exited the test van, and each participant was simultaneously issued an effervescent tablet, either 900 mg of NAC or placebo, which was dissolved in eight ounces of water. Randomization was done across participants based on the type of initial test in order to balance the distribution of NAC and placebo.

One participant from each group was issued a dosimeter (Quest Model 300) to automatically record the average level (dBA) of noise exposure during the two hours in the nightclub. All four participants of each group entered the nightclub together 30 minutes after taking their tablet. As they entered the nightclub, the dosimeter was turned on and the cover plate installed by a member of the test team. Each group was instructed to stay together and exit the nightclub after two hours. The groups were staggered such that each group entered the nightclub at 30-minute intervals.

As each group of participants exited the nightclub after two hours of exposure, a member of the test team met them and turned off the dosimeter. The participants immediately went to the test van for pure-tone and DPOAE testing. The test booth, examiner, and order of tests were consistent among the participants for pre- and postexposure testing. Participants were administered another Breathalyzer test after completion of the postexposure pure-tone and DPOAE measures in order to confirm that alcohol had not been consumed during the time spent in the nightclub.

Description of Tests

Pure-tone thresholds were obtained using two portable audiometers (Grason-Stadler, GSI-17) with standard headphones (TDH-39). For each test frequency, the right ear was tested first, followed by the left ear in the following order: 4, 3, 6, 2, and 8 kHz. Pure-tone measurements took approximately eight to ten minutes. Thresholds (dB HL) were recorded on individual tracking sheets identified only by assigned participant identification numbers. Pre-exposure tracking

sheets were sealed in an envelope immediately after completion of testing to prevent any influence on the collection of postexposure data.

DPOAEs ($2f_1$-f_2) were measured using two Otodynamic instruments (ILO 92 and ILO 88). Two different DPOAE paradigms were completed at each session. For the first paradigm, a frequency sweep method, the higher frequency primary, f_2, was varied at six points between 2 and 8 kHz (2, 3, 4, 5, 6, and 8 kHz) at a constant frequency ratio (f_2/f_1) of 1.2. Stimulus intensity levels were 60 and 50 dB SPL for f_1 and f_2, respectively. Using this procedure, DPOAE absolute amplitude and signal-to-noise ratio measures were obtained. The second paradigm was a ratio sweep, which yielded a group delay (msec) value, calculated from the slope of the distortion product phase versus distortion product frequency curve. For the ratio sweep, the higher frequency (f_2) stimulus was held constant at 4 kHz, and the lower frequency (f_1) stimulus varied so that the ratio (f_2/f_1) was swept between 1.1 and 1.3. This paradigm was performed at constant stimulus levels (60 and 45 dB SPL for f_1 and f_2, respectively). DPOAEs were collected in the right ear for both paradigms, followed by the left ear. All data were recorded on individual tracking sheets identified only by participant identification number, and the recordings were saved to files on the computer for later review.

RESULTS

One participant from Group 1 did not participate due to illness. Therefore, 15 participants were tested on the first night, and 16 participants were tested on the second night (n = 31). Both ears from the 31 participants (17 females and 14 males) were tested. Data were analyzed across all ears (62 ears). None of the participants failed the initial Breathalyzer or pregnancy tests, and none of the participants failed the postexposure Breathalyzer test. Fifteen participants received NAC, and 16 participants received the placebo. No side effects were reported by any of the participants during or following the study.

Dosimeter Readings

Dosimeter readings by group are shown in Table 1. All participants were inside the nightclub for two hours; however, there were differences in the accumulated noise exposure level across groups since groups entered the nightclub at different times. Participants in Group 1 were exposed to the highest level whereas participants in Group 5 were exposed to the lowest level. Across all groups, the average noise exposure level (L_{avg}) ranged from 92.5 to 102.8 dBA, with a mean of 98.1 dBA. The numbers of participants who received NAC or placebo within each group are included in Table 1.

Pure-Tone Thresholds

Pure-tone testing was initiated within five minutes of leaving the nightclub for those receiving the pure-tone test first, and there was about a 15-minute difference between those having pure-tone testing first and those having pure-tone testing second (after DPOAE testing). Pure-tone threshold change (TTS) was calculated by subtracting the pre-exposure threshold from the postexposure threshold. The mean TTS values are shown in Figure 1 as a function of initial test (pure-tone or DPOAE) and treatment (NAC or

Table 1. Dosimeter Readings by Subject Group and Distribution of Subjects (*n*) Receiving NAC or Placebo

Group #	1	2	3	4	5	6	7	8	Mean
Run Time (hrs.)	2:00	1:56	1:56	2:02	2:01	1:59	2:04	2:05	2:00
L_{avg} (dBA)	102.8	100.5	96.7	99.1	92.5	101.8	97.8	93.6	98.1
NAC (*n*)	2	2	2	2	2	1	2	2	
Placebo (*n*)	1	2	2	2	2	3	2	2	

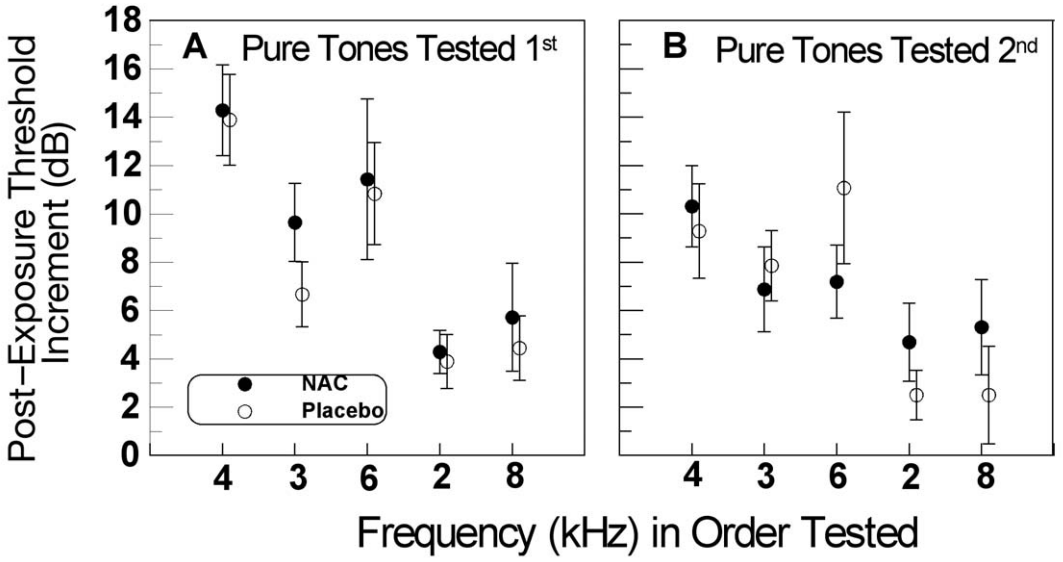

Figure 1. Mean and standard errors for pure-tone threshold changes for the NAC and placebo groups after two hours in the nightclub. Figure 1A represents the data from those participants who had pure-tone testing done prior to DPOAE testing. Figure 1B represents the data from those participants who had pure-tone testing done after DPOAE testing (approximately 15 minutes later). Data are collapsed across ears.

placebo) received. Repeated measures analysis of variance showed no significant ($p > 0.05$) interaction effects (frequency x treatment x initial test x ear) and no significant main effects for ear [$F(1, 54) = .0002$, $p = .989$], initial test [$F(1, 54) = 1.978$, $p = .165$], or treatment [$F(1, 54) = .299$, $p = .587$]. TTS as a function of frequency was significant [$F(4, 216) = 19.853$, $p = .000$], and Tukey post hoc analysis revealed that 4, 3, and 6 kHz were significantly different than 2 and 8 kHz. In general, greater amounts of TTS were found for 4, 3, and 6 kHz than for 2 and 8 kHz, regardless of whether pure-tone testing was done first (Figure 1A) or second (Figure 1B). When collapsed across treatment, the greatest TTS was at 4 kHz and averaged 14.1 dB for those having pure-tone testing first and 9.8 dB for those having pure-tone testing second. The mean TTS across all participants and frequencies was 7.6 dB.

DPOAE

DPOAE amplitudes were reviewed prior to analyses to be considered acceptable responses. The average noise floor level across frequency was -18.0 dB SPL. The criteria used for an acceptable pre-exposure DPOAE were an amplitude between -18.0 and 20.0 dB SPL and a signal-to-noise ratio (SNR) of 6 dB or greater. For postexposure DPOAEs, the amplitude had to be less than 20.0 dB SPL, and a minimum amplitude criterion was not imposed so that any reduction in amplitude would be included. To prevent exaggerated reductions, if the postexposure amplitude was less than -18.0 dB SPL, a value of -17.9 was assigned. All DPOAE amplitude data not meeting these criteria were eliminated. This resulted in some loss of DPOAE amplitude data, predominantly in the 5–8 kHz frequency range. The overall pre-exposure DPOAE amplitude across frequency for all individuals with acceptable data was 2.9 dB. The lowest pre-exposure DPOAE amplitude value included in the data set was -14.7 dB SPL, and there were only eight occurrences of DPOAE amplitude values between -10.0 and -14.7 dB SPL.

From acceptable emission data, amplitude changes were calculated by subtracting pre-exposure amplitude from postexposure amplitude (i.e., negative values indicate pre-exposure amplitudes were larger than postexposure amplitudes). Mean amplitude changes for the DPOAE frequency sweep are shown in Figure 2. A statistical analysis using a repeated measures design could not be performed for the complete set

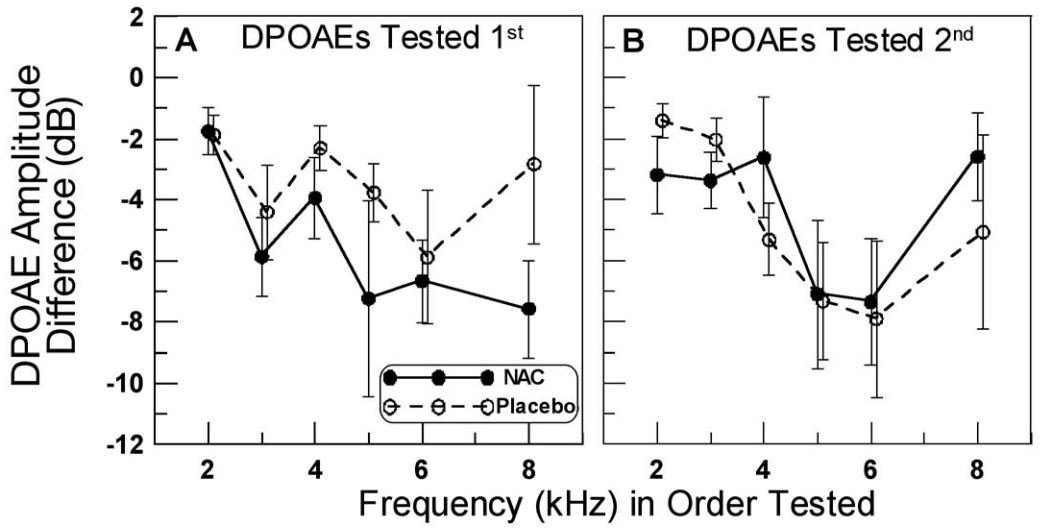

Figure 2. Mean and standard errors for DPOAE changes for the NAC and placebo groups after two hours in the nightclub. Figure 2A represents the data from those participants who had DPOAE testing done prior to pure-tone testing. Figure 2B represents data for those participants who had DPOAE testing done after pure-tone testing (approximately 15 minutes later). Data are collapsed across ears.

of frequency sweep data when all factors (treatment x initial test x ear) were included because there were too many missing data in the higher frequencies. Therefore, a repeated measures analysis of variance was performed for 2–4 kHz, which provided a more complete data set. No significant interactions were found, and the main effects were not significant for ear ($F[1, 44] = .008$, $p = .926$), initial test ($F[1, 44] = 1.403$, $p = .242$), treatment ($F[1, 44] = 1.435$, $p = .237$), or frequency ($F[2, 88] = 2.213$, $p = .115$). When ear was removed as a factor, a repeated measures analysis was able to be performed for all frequencies (2–8 kHz), and again there were no significant interactions, and the main effects were not significant for initial test ($F[1, 11] = .022$, $p = .883$), treatment ($F[1,11] = .905$, $p = .361$), or frequency ($F[5, 55] = 1.598$, $p = .175$). Postexposure DPOAEs were generally characterized by a decrease in amplitude. When collapsed across treatment for the 2–4 kHz region, mean amplitude differences were -3.46 dB for those who had DPOAE testing first and -2.97 dB for those who had DPOAE testing second. For the 5–8 kHz region, the amplitude differences were -5.63 dB for those who had DPOAE testing first and -6.30 dB for those who had DPOAE testing second.

Group delay differences were calculated by subtracting pre-exposure from postexposure values. Mean group delay differences, calculated for 4 kHz, are shown in Figure 3. These data are for 46 ears that remained following exclusion of those with missing data and group delay differences greater than 2 msec. No statistically significant results were found for group delay values for ear ($F[1, 37] = .042$, $p = .838$), initial test ($F[1, 37] = .054$, $p = .818$), or treatment ($F[1, 37] = 0.136$, $p = 0.714$). In general, the mean group delay values were 0.24 msec shorter following the noise exposure when DPOAEs were tested first, and 0.23 msec when DPOAEs were tested second.

DISCUSSION

In this study, the efficacy of NAC for protecting the ear from temporary changes following exposure to recreational music was evaluated. NAC was selected as the experimental treatment in this study because research has shown it to be effective in protecting ears exposed to loud noise in animal models, and it is available as an over-the-counter nutritional supplement with a favorable side effect profile (Kopke et al, 2000; Ohinata et al, 2003; Duan et al, 2004; Kopke

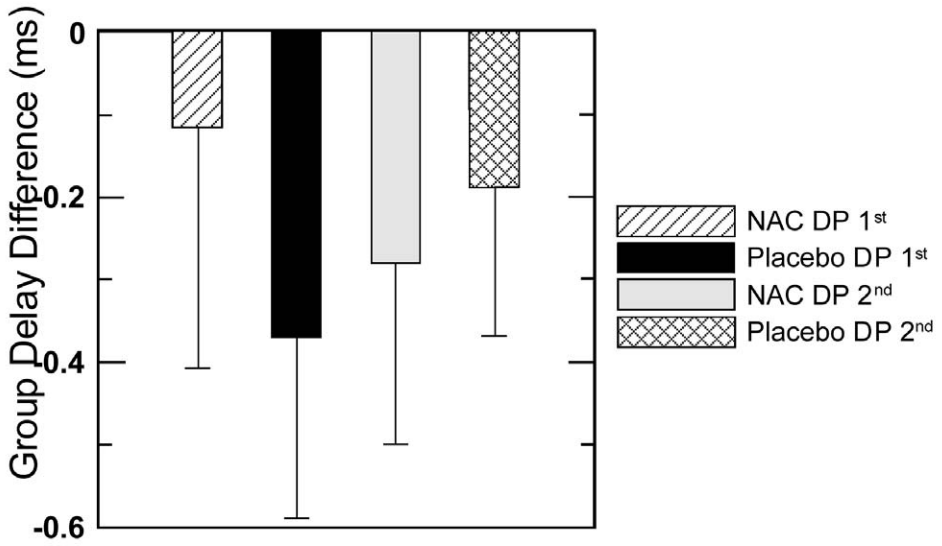

Figure 3. Mean and standard errors for group delay change at f_2 = 4 kHz.

et al, 2004). No statistically significant differences in pure-tone and DPOAE data were found between participants who received NAC and those who received the placebo. The nonsignificant benefit of NAC on pure-tone thresholds in the present study was consistent with the results from the only other known study that evaluated the relationship between NAC and noise exposure in humans (Toppila et al, 2002). The 900 mg NAC dosage used in this study was more than twice the dosage level used by Toppila et al. Additional studies in humans are needed to evaluate whether higher doses of NAC can provide any protection from noise exposure.

In animals, NAC treatment schedule and dose levels have been shown to be important factors. Kopke et al (2000) evaluated the effects of intraperitoneal injections of NAC (325 mg/kg) in chinchillas that were exposed to six hours of continuous octave band noise centered at 4 kHz and presented at 105 dB SPL. They found NAC to be more effective in protecting chinchillas from threshold shifts when they were administered NAC before and after noise exposure when compared to chinchillas that only received NAC after the noise exposure. Initial threshold shifts (one hour following exposure) were less in the group that received NAC before and after exposure in comparison to the group that only received NAC after the exposure and the saline injected control group. All three groups showed recovery of threshold shifts; however, the saline control group had significantly greater permanent threshold shifts by two weeks than the pre-post NAC treated group. The pre-post NAC treated group continued to show recovery, and at three weeks had less than 10 dB threshold shifts. Corresponding hair cell counts at three weeks showed 60–80% outer hair cell loss in the saline control group and substantially less (20–30%) outer hair cell loss in the pre-post NAC treated group. The Kopke et al study did not do histological examinations that would reflect damage during the immediate postexposure time, during which TTS may have been involved, nor did they evaluate the condition in which NAC was only given prior to exposure, as was done in the current study. Kopke et al (2004) examined the effectiveness of NAC at different dosage levels (325, 200, 100, and 50 mg/kg) in chinchillas and determined that NAC was still quite effective at the lowest dose of 50 mg/kg. The authors suggested that the use of clinically available antioxidant compounds may be effective in protecting the ear from acute acoustic injury.

Duan et al (2004) varied the administration schedule and number of doses of NAC in rats exposed to impulse noise. At four weeks postexposure, they found less PTS and hair cell damage than the control group (no NAC) when NAC (350 mg/kg) was administered one hour prior, immediately post, and three hours post-noise-exposure. When additional doses

were administered 24 hours prior and 24 hours post-noise-exposure, the rats showed greater amounts of PTS, as well as more outer and inner hair cell loss than the control group and the group with only the three dosages of NAC. Ohinata et al (2000) reported that ROS production from noise trauma was greatest five hours post-noise-exposure. Duan et al (2004) suggested that taking NAC prior to exposure may even interfere with the production of endogenous antioxidants.

In the present study, the administration of NAC 30 minutes prior to noise exposure was not found to produce any significant benefit for TTS. Duan et al (2004) also reported that the effects of NAC on TTS were complicated. They reported significantly less TTS at 4 kHz one hour after noise exposure for the group with three administrations of NAC compared to the control group, as well as the group with five administrations of NAC, but found no differences in TTS between any of the groups one day after exposure. Subsequent to day one, different rates of recovery were found for the different groups.

Cochlear damage resulting from PTS and TTS may have different underlying mechanisms and may involve the disruption of the mechanical process and/or the metabolic activity (Nordmann et al, 2000; Duan et al, 2004). Nordmann et al (2000) found that TTS was characterized by buckling of pillar cells and lack of OHC stereocilia contact with the tectorial membrane, whereas PTS showed hair cell and nerve fiber loss. TTS may not produce the same oxidative stress that occurs with PTS (Kopke et al, 2002); hence, the beneficial effects of NAC may be less apparent for TTS than for PTS. In the aforementioned animal studies, even though there was some recovery of thresholds over time, the nontreated control animals ended up with permanent threshold shifts; therefore, it is not known whether the beneficial effect of NAC obtained immediately postexposure was related to mechanisms of TTS or PTS. Since the present study only examined TTS, comparison to these animal studies may be difficult.

There was some variation in the exposure levels in the nightclub that occurred over each night of the testing. The levels of music found in the present study ranged from 92.5–102.8 dBA and are similar to those levels reported for nightclubs by others (Liebel et al, 1996; Gunderson et al, 1997; Toppila et al, 2002; Bray et al, 2004). Although each group spent two hours inside the nightclub, there were four groups staggered over a three and one-half hour period on each of the two test nights. On each of the test nights, the nightclub hosted various bands that performed live throughout the night, and the bands varied in their preferred volume of playing. Ideally, all participants would be exposed to the same two-hour period; however, this was not attempted in the current study because it was not possible to simultaneously test more than four participants at one time, and due to the quick recovery of TTS following the cessation of exposure to noise, the importance of obtaining postexposure results immediately after the participants exited the nightclub took precedence in this study. A therapeutic effect of NAC may not have been evident due to this uncontrolled variability in noise exposure levels. It is also possible that the noise levels were too high for the chosen dosage level of NAC, rendering it ineffective, or that the noise levels were too low for the ear to require additional GSH to offset any overabundance of ROS.

Overall, the trend for the pure-tone data showed that the amount of TTS changed across frequency. Greater amounts of TTS were recorded for 4, 3, and 6 kHz than for 2 and 8 kHz, and these differences were statistically significant. This was expected because the 3–6 kHz range is known to be most susceptible to noise exposure (Cooper and Owen, 1976). One should consider the influence of time in obtaining thresholds following exposure to noise, since some recovery is expected to occur. It is possible that the amount of TTS at 3 and/or 6 kHz could have been greater if they had been tested first. The average TTS was 14.1 dB at 4 kHz for those who received pure-tone testing prior to DPOAE testing and 9.8 dB for those who had pure-tone testing after DPOAE testing; however, these were not significantly different. The average TTS values obtained at 4 kHz in this study are slightly higher than those reported by Toppila et al (2002), even though their participants were exposed for a four-hour time period, but with average sound levels that were slightly less than in the current study. Similar to the present study, Liebel et al (1996) found the greatest amount of TTS at 4 kHz for participants exposed to one hour of nightclub music (105

dBA). Liebel et al also reported a mean TTS of 10.1 dB across all frequencies after two hours of exposure, which is slightly greater than the overall mean TTS of 7.6 dB across all frequencies in the present study. Additionally, the pure-tone data from the current study were reviewed by imposing a criterion of 10 dB or greater to represent a significant change for TTS. Using this criterion, it was found that TTS occurred in 44, 71, and 55% of ears for 3, 4, and 6 kHz, respectively. There were no significant differences between the number of ears demonstrating 10 dB or greater TTS between the NAC and placebo groups using chi-square analyses for any of the frequencies.

Generally, there was a decrease in DPOAE amplitudes following noise exposure. This is consistent with the findings of Liebel et al (1996) who evaluated the effectiveness of DPOAEs in detecting threshold shifts following exposure to disco music. In the present study, when a criterion DPOAE amplitude reduction of greater than 2 dB was imposed on the data, 46, 63, and 61% of the ears met this criterion for 2, 3, and 4 kHz, respectively. There were no significant differences between the number of ears demonstrating amplitude reductions greater than 2 dB between the NAC and placebo groups using chi-square analyses for any of the frequencies.

When comparing pure-tone TTS and DPOAE reductions at 3 kHz, of the 27 ears that had pure-tone TTS of 10 dB or greater, 19 ears (70.4%) had DPOAE amplitude reductions greater than 2 dB. At 4 kHz, of the 44 ears that had TTS of 10 dB or greater, only 26 ears (59.1%) showed DPOAE amplitude reductions of greater than 2 dB. In the present study, there were also ears that showed DPOAE amplitude reductions, but did not show any pure-tone threshold shifts. At 3 kHz, of the 39 ears with amplitude reductions greater than 2 dB, only 19 ears (47.4%) showed TTS of 10 dB or greater. At 4 kHz, of the 35 ears with amplitude reductions greater than 2 dB, there were 26 ears (74.3%) that showed TTS of 10 dB or greater. Liebel et al (1996) reported that reductions in DPOAE amplitude did not occur in all participants exhibiting TTS and concluded that DPOAE testing was not ideal for the detection of temporary changes in auditory function due to noise exposure in comparison to pure-tone testing. However, there are noise exposure studies in humans and animals demonstrating evoked otoacoustic emission reductions without threshold shifts (Lucertini et al, 2002; Davis et al, 2005). Others have reported changes in auditory function identified earlier with evoked otoacoustic emissions versus hearing threshold measures when exposed to cis-platinum (Plinkert and Krober, 1991; Sie and Norton, 1997). This conflicting evidence suggests further studies comparing the sensitivities of pure-tone measures and DPOAEs to the effects of noise exposure in humans.

For DPOAE group delay, while not significant, there was a trend toward slightly shorter values following noise exposure. This is consistent with Engdahl and Kemp (1996), who found that after exposing participants to a brief narrow band noise, participants had slightly shorter group delay values, although not significantly different from pre-exposure values. However, Namyslowski et al (2004) found longer group delay values in miners with long-term histories (8–15 years) of exposure to occupational noise than for healthy young adults. Expectations for DPOAE group delay may depend on the duration of exposure and/or underlying physiologic consequences of noise exposure. Telischi et al (1998) found that changes in group delay occurred much sooner (1–5 seconds) than DPOAE amplitude changes (15–30 seconds) following interruption of cochlear blood flow. Ohinata et al (2003) have shown that noise-induced cochlear damage may be associated with increases of 8-isoprostane formation, and Miller et al (2003) have suggested 8-isoprostane formation can lead to attenuation of cochlear blood flow.

SUMMARY

Using a single dose of NAC (900 mg) taken 30 minutes prior to the noise exposure, no significant differences were found between those participants taking NAC and those taking the placebo for any of the measures. Additional studies in which the dosage level and/or schedule of administration are varied may be warranted in order to determine if there is any potential benefit of this antioxidant in protecting ears from TTS.

Across all participants, the levels of music/noise exposure recorded in the nightclub ranged from about 93 to 103 dBA over the two nights of the study. For a two-hour exposure to the noise, the maximum mean TTS was found to be 14 dB at 4 kHz

when pure-tone measures were obtained immediately after the noise exposure (tested before DPOAEs). DPOAE measures were characterized by about a 5 dB amplitude reduction and a trend towards a shorter group delay value when measured immediately after the noise exposure (tested before pure tones). When imposing specific criteria of 10 dB or greater for pure-tone threshold shifts and greater than 2 dB DPOAE amplitude reductions, pure-tone shifts occurred more often at 4 kHz, and DPOAE reductions occurred more often at 3 kHz. Future studies measuring damage due to noise exposure should consider using both types of measures.

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