N-Acetyl-cysteine against noise-induced temporary threshold shift in male workers

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Abbreviations: GPX, Glutathione peroxidase; GSH, Glutathione; GSR, Glutathione reductase; GST, Glutathione S-transferase; HF, High frequency; HL, Hearing threshold level; HPD, Hearing protection device; IRB, Institutional Review Board; ISO, International Organization for Standardization; LF, Low frequency; NAC, N-Acetyl-cysteine; NIHL, Noise-induced hearing loss; PTA, Pure-tone audiometry; PTS, Permanent threshold shift; RNS, Reactive nitrogen species; ROS, Reactive oxygen species; TTS, Temporary threshold shift; TWA, Time-weighted average.

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1. Introduction

It is estimated that 10–15 million Americans have noise-induced hearing loss (NIHL) (Niskar et al., 1998; Nelson et al., 2005). Worldwide, 16% of the disabling hearing loss in adults results from excessive exposure to noise in the workplace. The incidence of NIHL is highest among noisy occupations such as military, construction, manufacturing, and mining (Nelson et al., 2005).

While multiple factors contribute to the occurrence of occupational NIHL, the lack of protection is a main contributor. People are encouraged to use personal hearing protection devices (HPDs) but these devices prove insufficient in many situations such as highly noisy environments, noncompliant workers, poor fit, frequent head movement required by the jobs, discomfort, and reduced communication ability (Rovig et al., 2004).

A number of studies have reported that the mechanisms of NIHL are not just mechanical or physical in nature, but that cochlear injury may also be metabolically induced (Lim and Melnick, 1971; Lim and Dunn, 1979; Slepecky, 1986; Yamasoba et al., 1998).

Previous animal studies showed protective effects of antioxidant medicines against noise-induced hearing loss (NIHL). It is unclear whether antioxidants would protect humans from NIHL. We conducted a study to determine whether N-Acetyl-cysteine (NAC) protected men against noise-induced temporary threshold shift (TTS), and whether subgroups with genetic polymorphisms of glutathione S-transferase (GST) T1 and M1 responded to NAC differently. In this prospective, double-blind, crossover study, 53 male workers were randomly assigned to receive either NAC (1200 mg/day, 14 days) during the first period and placebo during the second period, or placebo during the first period and NAC during the second period. Dosing periods were separated by a washout period of 2 weeks. The hearing threshold changes were determined before and after each dosing period. Pre-shift hearing threshold for high frequencies was 19.1 dB. Daily exposure to noise ranged from 88.4 to 89.4 dB. The noise levels of different frequencies ranged from 80.0 to 89.4 dB with a peak-value at 4 kHz. NAC significantly reduced TTS ($p = 0.03$). When the participants were grouped by GST M1,T1 genotypes, the NAC effect was only significant among workers with null genotypes in both GSTM1 and GSTT1 ($p = 0.004$). NAC may prevent noise-induced TTS among occupationally noise-exposed men. The protective effect of NAC was more prominent in subjects with both GSTM1-null and GSTT1-null genotypes.

keywords: hearing loss; antioxidant; NAC; genetic polymorphism; glutathione S-transferase

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in auditory hair cells, including the cell membrane and the intracellular biochemical pathways (Kopke et al., 1999). These changes evoke the formation of free radicals such as reactive oxygen (ROS) and nitrogen (RNS) species that can overwhelm resident detoxification and antioxidant mechanisms (Yamane et al., 1995; Clerici and Yang, 1996).

There are several potential mechanisms at the cellular level underlying noise-induced temporary threshold shift (TTS) (Henderson et al., 2006). During high-level noise exposure, the inner hair cells are highly active, leading to the release of large amounts of glutamate into the synapse with the auditory nerve fibers. The levels of glutamate in the synapses can overstimulate the glutamate receptors on the postsynaptic cells, and cause a dramatic swelling of afferent dendrites. Over time, the swollen or ruptured dendrite terminals appear to recover and begin to function normally (Robertson, 1983). During a noise exposure, the electron transport chain of the mitochondria uses large amounts of oxygen to meet increased cellular demands for energy, which can then create large amounts of superoxide generated as an unwanted byproduct (Halliwell and Gutteridge, 1999). The increased superoxide can then react with other molecules to generate higher levels of other ROS in the cochlea. These molecules can contribute to the hair cell lesions and loss of function seen after noise. In normal functioning mitochondria, ROS and free radicals are subsequently neutralized by conversion into O₂, CO₂, or H₂O. It suggest that the above two types of damage may contribute to TTS.

One major intracellular antioxidant pathway of NIHL involves the tripeptide glutathione (GSH) (Meister, 1991). Noise decreases the level of GSH and increases the level of oxidized glutathione in the inner ear, leaving it prone to ROS-mediated cell damage (Yamasoba et al., 1995). Replenishment of GSH with a prodrug such as N-acetyl-cysteine (NAC) or an ester of GSH can reduce hearing loss from loud noise in experimental animals (Ohinata et al., 2000; Hight et al., 2003; Kopke et al., 2005; Wu et al., 2010). NAC provides a substrate for cochlear GSH synthesis (Ohinata et al., 2000). Based on the previous animal studies, we can predict that NAC is acting relative to the above-mentioned mechanisms of TTS. Penugonda et al. (2005) showed that NAC reduced glutamate-induced ROS elevations, consequently preserving intracellular GSH. NAC administration was also found to protect stress-induced mitochondrial injury in a rat model (Cocco et al., 2005). It is thus possible that NAC might protect noise-exposed humans from acoustic injuries to the cochlea, despite a lack of any direct evidence from a randomized clinical trial (Lynch and Kil, 2005; Kopke et al., 2007).

Once absorbed, NAC undergoes de-acetylation in the liver or local tissues to form l-cysteine, which in turn enhances GSH production (Meister, 1991). NAC has been used in the clinical setting safely for over 15 years as an antidote to acetaminophen overdose and as a mucolytic agent for respiratory infection (Kelly, 1998). NAC is well tolerated by healthy individuals when taken orally at 1–3 gm per day (Lynch and Kil, 2005). The plasma half-life of free NAC is estimated to be about 2.2 h. Virtually no NAC is detectable 10–12 h post-administration (De Caro et al., 1989).

Glutathione S-transferases (GSTs) are multigene family of detoxification enzymes which catalyze the conjugation of GSH with xenobiotics and other compounds and detoxify these chemicals. Since GSTs help the hair cells resist oxidative damage, GST enzymes are considered to play an important role in the antioxidant protection of the cochlea (Yamasoba et al., 1998; Rabinowitz et al., 2002; Carlsson et al., 2005; Yang et al., 2005). In both GSTT1 and GSTM1, genetic polymorphisms involving the deletion of 20 base pairs, respectively, result in very low activities in their enzymes and possibly the interference of GSH-related detoxification (Seidegard et al., 1986; Pemble et al., 1994; Wiencke et al., 1997; Bruhn et al., 1998). These two putative high-risk genotypes might render the individuals more prone to oxidative damage and possibly more susceptible to NIHL. According to the above-mentioned animal studies, NAC could up-regulate the GSH synthesis (Ohinata et al., 2000). Therefore, supplement of the GSH prodrug NAC may exert significant effects among those with GST-null genotypes.

In this study, we examined whether noise-induced TTS could be significantly reduced by the prophylactic oral administration of NAC in a prospective, randomized double-blind crossover trial. We further examined whether GST genetic variants predisposed some of the subjects to the beneficial effects of NAC treatment.

2. Materials and methods

2.1. Study patients

This study was performed according to the guidelines in the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of National Taiwan University Hospital, Taipei. Informed consent was obtained from all study participants.

We recruited male volunteers who had been employed for at least 1 year from a steel manufacturing company in southern Taiwan. Their noise exposure is recorded annually at industrial hygiene assessments. In the Department of Equipment Repair and Maintenance, the measured noise exposure was approximately 90 dB for the past 3 years. All of the workers who worked in the day shift in this department were invited to participate in this study. Consent to participate in this study was obtained from all of the workers in this department. Those with possible exposure to organic solvents or polycyclic aromatic hydrocarbons were excluded. In addition, subjects with any of the following histories were also excluded: head injury, otological disease, other diseases that could affect hearing, previous or present treatment with ototoxic drugs, long-term (>6 months) use of vitamins and nutritional supplements, potentially harmful noise exposure during leisure time or during their military service, or a family history of congenital deafness.

2.2. Study design

This study used the standard 2 × 2 crossover design. Each subject was randomly assigned to either sequence 1 (NAC first) or sequence 2 (placebo first). Subjects in sequence 1 receive formulation NAC (1200 mg/day, 14 days) (Actein, Synmosa Corp., Taiwan) during the first intervention period and placebo (a tablet of identical taste and odor to the NAC agent) during the second intervention period. Subjects in sequence 2 receive placebo during the first intervention period and formulation NAC during the second intervention period. Intervention periods are separated by a washout period of 2 weeks (Fig. 1). During both intervention phases, the participants were briefly asked if the formula had any adverse effect at each assessment.

2.3. Assessment measures

The assessments, which were performed during one regular day of work, included structured interviews, otoscopic examinations, pre- and post-shift pure-tone audiometry (PTA), and personal noise measurements. Venous blood for DNA extraction was also collected on the same day.

2.4. Questionnaire

A structured questionnaire was used to solicit information about demographic characteristics, work history, health habits (smoking
and alcohol drinking), medical conditions, noise exposure, and the uses of medications, dietary supplements and hearing protection.

2.5. Noise exposure measurement

Personal noise exposure was assessed from 7 a.m. to 3 p.m. during the work shift using the TES-1355 Noise Dose Meter (TES Electrical Electronic Corporation, Taipei, Taiwan). Frequency characteristics of noise were measured using TES-1358 Sound Analyzer (TES Electrical Electronic Corporation, Taipei, Taiwan) with 1/3 octave band analysis. They used half-inch, free-field condenser microphone with frequency range from 31.5 Hz to 8 kHz. During this work shift, the participants did not use hearing protection devices.

2.6. Assessment of hearing status

Before receiving the audiological assessment, the participants were asked to avoid explosive noise exposure for at least 48 h. An otolaryngologist (C.Y. Lin) conducted otoscopic examinations to determine the outer/middle ear status.

An audiologist obtained PTA for all subjects in a sound-attenuating chamber with a background noise level of ≤25 dB, which is compatible with the criteria of International Organization for Standardization (ISO) 8253-1 (ISO, 1989). For each ear, the test frequencies included 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz. The hearing threshold level (HL) for high frequencies (HF) by PTA (HF PTA) was defined as the average of HFs at 3000, 4000, and 6000 Hz for each ear examined. The HL for low frequencies (LF) by PTA (LF PTA) was defined as the average of HFs at 500, 1000, and 2000 Hz. A total of four hearing assessments by PTA were completed for each formulation period on the 1st day pre- and post-shift, and the 14th day pre- and post-shift (Fig. 1). The amount of TTS was calculated by subtracting the pre-shift hearing threshold from the post-shift hearing threshold at each frequency.

2.7. Genotyping of GST polymorphisms

Venous blood samples were collected in heparinized tubes at the worksite and placed immediately in a refrigerated container. Genomic DNA was extracted from all blood samples using standard phenol/chloroform extraction techniques. The GSTM1 and GSTT1 genes were determined simultaneously in a single assay using the multiplex PCR approach described by Arand et al. (1996).

2.8. Statistical analysis

Some earlier studies have shown that animals and humans with a previous permanent threshold shifts (PTS) showed lower TTS to
a further noise exposure, compared with subjects with no previous history of noise exposure (Ward, 1973; Perez et al., 2004). Therefore, those with preexisting hearing damage, i.e. permanent threshold shift of greater than 50 dB in either low frequency areas or high frequency areas on the 1st day of study, were excluded from the analysis.

The quantitative variables were analyzed by Student’s t-test while the categorical variables were analyzed by Chi-square test. Analysis of the bioequivalence on TTS at HF between two formulations (NAC and the placebo) was carried out using analysis of variance (ANOVA) for the different combinations of GSTT1 and GSTM1 genotypes.

Most calculations were computed using the statistical software R (Hornik, 2009). A two-tailed P value of less than 0.05 was considered to indicate a significant difference.

3. Results

A total of 60 workers voluntarily participated in this study. However, 6 workers had preexisting hearing loss of >50 dB for high frequencies and 1 worker accidentally turned off the noise monitoring device. These 7 participants were excluded from the analysis. The 53 workers who satisfactorily completed the study (53/60, 88.3%) (Table 1) had worked in this steel factory for an average of 16.3 years. Most of them were middle-aged. During the days of TTS measurements, the average daily noise exposure (time-weighted average in 8 h, TWA-8 hours) ranged from 88.4 to 89.4 dB by personal noise monitoring (Table 1). Other demographic and personal characteristics were not significantly different between sequence 1 (NAC first) and sequence 2 (placebo first). The frequency range of the noise in the workplace was as follows, 81.2 dB at 31.5 Hz, 80.0 dB at 63 Hz, 81.3 dB at 125 Hz, 85.3 dB at 250 Hz, 89.0 dB at 500 Hz, 88.3 dB at 1 kHz, 89.0 dB at 2 kHz, 89.4 dB at 4 kHz and 87.9 dB at 8 kHz.

The hearing threshold levels for both ears were tested and analyzed to determine the average hearing threshold for each participant. Prior to treatment, the pre-shift hearing threshold at HF was 19.3 dB HL, with no difference between the sequences. For all participants exposed to noise, the mean TTS at HF was 2.77 dB after placebo, and 2.45 dB after NAC (p = 0.03) (Table 2). These data indicate reduced threshold shift by NAC based on ANOVA for a 2 x 2 crossover design. Effects caused by carry-over and period were non-significant. The TTS at LF were not significantly different (p = 0.88) between the post-placebo and post-NAC phases of study.

Genotypic determination showed that GSTM1-null and GSTT1-null accounted for 57% and 57% of the subjects, respectively. Twenty of the 53 (37.7%) subjects harbored both GSTM1-null and GSTT1-null genotypes (Table 1). The direct drug effect on HF was more prominent among such subjects (p = 0.004). However, among other participants with a non-null genotype in GSTT1 or GSTM1, there was no significant difference in TTS at HF (p = 0.92). ANOVA for a 2 x 2 crossover design showed no significant carry-over effect or period effect.

Each participant was asked about the side-effects during and at the end of the study. No adverse side-effects related to NAC or the placebo were reported.

4. Discussion

This study demonstrated that noise-induced TTS at HF could be reduced by prophylactic oral administration of the antioxidant NAC at 1200 mg/day for 14 days. Furthermore, such effects were more prominent among men carrying both GSTM1-null and GSTT1-null genotypes.

### Table 1

<table>
<thead>
<tr>
<th>Demographic and personal characteristics (n = 53, male)</th>
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<tbody>
<tr>
<td>Quantitative variable</td>
</tr>
<tr>
<td>Age (years)</td>
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<td>Employment (years)</td>
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<tr>
<td>Body Mass index (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
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<tr>
<td>Smoking tobacco (pack-year)</td>
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<tr>
<td>Personal noise exposure (TWA-8 hours) (dBA)</td>
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<tr>
<td>Pre-NAC</td>
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<tr>
<td>Post-NAC</td>
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<td>Pre-Placebo</td>
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<tr>
<td>Post-Placebo</td>
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<tr>
<td>Pre-shift LF PTA&lt;sup&gt;b&lt;/sup&gt; (dB HL)</td>
</tr>
<tr>
<td>Pre-NAC</td>
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<tr>
<td>Pre-Placebo</td>
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<tr>
<td>Pre-NAC</td>
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<tr>
<td>Pre-Placebo</td>
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<tr>
<td>Categorical variable</td>
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<tr>
<td>Drinking alcohol</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Smoking tobacco</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
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<td>GSTT1</td>
</tr>
<tr>
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<tr>
<td>Wild</td>
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<tr>
<td>GSTM1</td>
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<tr>
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<tr>
<td>Wild</td>
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<tr>
<td>GSTT1 + GSTM1</td>
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<tr>
<td>Null/Null</td>
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<tr>
<td>Null/Wild + Wild/Wild</td>
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</tbody>
</table>

<sup>a</sup> S.D.: standard deviation.
<sup>b</sup> Student’s t-test.
<sup>c</sup> Chi-square test.
<sup>d</sup> The average of hearing threshold levels at 500, 1000, and 2000 Hz by pure-tone audiometry (PTA).
<sup>e</sup> The average of hearing threshold levels at 3000, 4000, and 6000 Hz by pure-tone audiometry (PTA).

To date, some preliminary human clinical trials have been conducted to evaluate the safety and efficacy of NAC in reducing noise-induced auditory changes. In a randomized, double-blind, placebo-controlled study, 31 normal-hearing participants (mean age = 22.0 years) were dosed orally with placebo or 900 mg NAC 30 min prior to visiting a local nightclub where they were exposed to 2 h of live music. The average noise exposure level ranged from 92.5 to 102.8 dB, with a mean of 98.1 dB. No statistically significant differences in TTS between the two groups were found (Kramer et al., 2006). The lack of differences might be attributable to (1) the low NAC dosage (900 mg) was insufficient for protection; (2) the fact that NAC was given only once (30 min prior to the noise exposure). Such dosing might cause the glutathione concentration in the inner ear to be lower than the effective level. In comparison, our participants received a higher dose for longer duration (1200 mg/day, 14 days), and a protective effect on TTS was observed.

In a double-blind, placebo-controlled study involving 566 young and healthy US Marine recruits, 900 mg NAC was dosed orally, 3 times a day for 2 weeks to reduce noise-induced PTS during routine weapons training (Lynch and Kil, 2005; Kopke et al., 2007). According to the review article, preliminary results of the study suggested safety of NAC and some beneficial effects on reducing noise-induced PTS in the soldiers (Kopke et al., 2007).
The effects of NAC and placebo on low- (LF) and high-frequency (HF) temporary threshold shifts (TTS) from workplace noise.

<table>
<thead>
<tr>
<th></th>
<th>LF^a</th>
<th>P value^b</th>
<th>HF^a</th>
<th>Post-Placebo</th>
<th>Post-NAC</th>
<th>P value^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants (n = 53)</td>
<td>0.9 ± 2.9^c</td>
<td>0.88</td>
<td>2.8 ± 2.9^d</td>
<td>2.3 ± 3.6</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>GSTT1 + GSTM1</td>
<td>1.0 ± 3.1</td>
<td>0.47</td>
<td>3.1 ± 3.1</td>
<td>1.2 ± 3.6</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Null/Null (n = 20)</td>
<td>0.8 ± 2.9</td>
<td>0.81</td>
<td>2.6 ± 2.9</td>
<td>3.2 ± 3.4</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Null/Wild + Wild/Wild (n = 33)</td>
<td>1.3 ± 2.7</td>
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</table>

^a LF: low frequency; HF: high frequency.
^b Analysis of variance (ANOVA) for a 2 × 2 crossover design. Effects caused by carry-over and period were non-significant for overall, null/null, and other genotypic combinations.
^c Values are means ± standard deviation.

Table 2

Despite the large number of studies, there are a number of findings which have led to different hypotheses concerning mechanisms of noise damage. Structural and/or biochemical alterations (e.g., breakage of stereocilia tip links, pillar buckling, ROS increasing) have been proposed as a correlate of TTS. Some previous studies have described changes in hair cell stereocilia, such as collapse, fusion, fracturing of the roots and complete loss, as correlates of PTS (Nordmann et al, 2000). It appears that TTS and PTS are produced by different mechanisms. Quirk et al. (1994) suggested that lipid peroxidation might be a cellular mechanism of NIHL. Lipid peroxidation is a process through which ROS and free radicals break down lipid molecules, such as those in the membrane of a cell (Henderson et al, 2006). It is a self-perpetuating reaction. ROS and free radicals (superoxide, the hydroxyl radical, and the peroxynitrite radical) may produce more ROS and free radicals (hydrogen peroxide, ozone) (Halliwell and Gutteridge, 1999). As stated previously, NAC is a broad spectrum antioxidant which can scavenge hydrogen peroxide and hydroxyl radicals. It may be also an inhibitor of lipid peroxidation. In an animal study, Ohnata et al. (2003) showed that pretreatment with NAC significantly reduced noise-induced PTS and attenuated both outer and inner hair cell loss. Although the present human study revealed that NAC had attenuated noise-induced TTS, its effects could not be extrapolated to PTS. Whether PTS in humans can be reduced by NAC warrants further investigation.

In this study, we examined whether GST genetic variants were modifier factors for prophylactic NAC treatment of NIHL and found that NAC provides more prominent beneficial effects especially to workers with both GSTM1- and GSTT1-null genotypes. Null genotype in either GSTM1 or GSTT1 render markedly low, but not completely absent, GST protein activity (Fujimoto et al, 2006, 2007). However, GST enzymes are not the only antioxidant enzymes. Other enzymes such as selenium-dependent Glutathione peroxidase (GPX1) and Glutathione reductase (GSR), which are involved in the recycling of oxidized GSH, provide substrates for GST. In both GPX1 knockout mice and normal mice on selenium-deficient diets, GPX1 activity was markedly reduced while GST activities were enhanced, indicating a compensatory mechanism in antioxidant (Cheng et al, 1997; Ho et al, 1997; Ohlemiller et al, 2000). Therefore, we speculate that the activities of other antioxidant enzymes might be comparatively high in the cochlea of GSTM1-null and GSTT1-null men, as a compensatory mechanism for low GSTM1 and GSTT1 activities. Once a large dose of NAC was given to individuals with both null genotypes, the increase in the level of GSH substrate, cysteine, may greatly enhance the reaction of glutathione conjugation, resulting in elevated antioxidant activity compared to that of individuals with any other combination of the genotypes. Functional studies are required to verify these speculations.

In this factory with the average daily noise exposure ranging from 88.4 to 89.4 dB, the amount of TTS was not very large. However, among workers carrying both GSTM1-null and GSTT1-null genotypes, the noise exposure produced a small (3.1 dB) threshold shift with placebo treatment, while there was a 1.2 dB threshold shift with NAC treatment (Table 2). Despite a concern that determining pure-tone thresholds in humans is generally accurate to within ±3 dB, larger study population would allow for detection of smaller effects. In this study, design of a randomized double-blind study with crossover protocol prevented biased assessment of the thresholds. Therefore, we believe the observed 1.9 dB difference in HF threshold shifts between placebo and NAC groups is real, and is a significant (~61%) attenuation of the noise effects on TTS.

The strengths of the present study include (1) the crossover design which allows the participants to be compared to themselves in terms of hearing threshold changes either after placebo or after NAC; (2) personal monitoring of noise showing workers’ exposure at a TWA range around 88.4 – 89.4 dB; and (3) examination of gene—environment interaction by considering both GSTM1 and GSTT1 genotypes.

Our study has several limitations. Firstly, the small number of subjects limited the ability to generalize the findings. Secondly, the narrow range of noise exposure made it difficult to document a dose—response relationship. Therefore, the range of noise exposure that was protetable by NAC could not be determined. Thirdly, only one dose was given to the workers for a fixed duration. Thus it was impossible to determine whether a smaller dose might also prove effective. Further human studies involving a larger number of individuals exposed to a wider range of noise and different dose regimens are warranted.

Use of the prodrug of glutathione to prevent noise-induced hearing loss is one form of chemoprevention. Chemoprevention has been applied widely, mainly against the outcomes of infectious conditions or malignancies. Among infectious conditions, acquired immunodeficiency syndrome, malaria, influenza, group B streptococcal infections, surgical and dental infections, respiratory syncytial virus infection are frequent targets of chemoprevention. As for malignancies, recent developments involved chemoprevention of human cancers such as lung, colon, and liver. Our findings demonstrate a potentially broadened application of chemoprevention in hearing loss caused by occupational noise. Such novel application will likely expand the concept and usefulness of chemoprevention and benefit public health.

NAC pretreatment was found to reduce somewhat the TTS that was sustained among noise-exposed workers. Such protective effects were more prominent among workers with both GSTM1-null and GSTT1-null genotypes. These findings extend previous research indicating that NAC is protective against loud continuous noise and demonstrated the feasibility of reducing noise-induced hearing loss using NAC.
Acknowledgments

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References


