REVIEW

Mechanisms of ototoxicity by chemical contaminants: Prospects for intervention

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OSHA has promulgated noise exposure standards (29 CFR 1910.95) and established regulations for hearing conservation programs (Hearing Conservation Amendment [46 Fed. Reg. 4078 (1981); 48 Fed. Reg. 9776 (1983)]) designed to protect workers in many occupations from noise induced hearing loss (NIHL). However, the promulgation of these standards has not eliminated NIHL as one of the 10 most common workplace "diseases" in the US (CDC, MMWR, 1986) or "the most" common workplace disease (US Dept. HHS, NIOSH, 1996). In one extreme example, a NIOSH Health Hazard Evaluation Report (HHE88-0290-2460) cited by Tubbs (1995), reported that audiometric studies of over 400 firefighters showed normal hearing in only 40% of those employed less than 6 years with no normal audiograms found in those employed more than 20 years. Tubbs (1995) notes that NIHL in this population exceeds that which would be predicted based upon noise exposure data. Among explanations offered for this difference include inadequacy of the 5 dB exchange rule (by which sound intensity may be increased by 5 dB when noise duration is cut in half), the narrow band of noise generated by critical noise sources such as sirens, and the interaction of toxicants at the fire site with noise exposure.

There are many different reasons why occupational noise exposure still produces profound health deficits. These include problems of accurate noise characterisation, problems in equating noise exposures of varying time durations using the "equal-energy principle" (selection of an appropriate relationship between duration and intensity of exposure), and significant individual (and idiopathic) differences in susceptibility that might relate to genetic factors and to unrecognised environmental factors. This paper focuses on one such environmental factor that has not received adequate attention; the potentiation of NIHL by simultaneous exposure to chemical ototoxicants such as chemical asphyxiants, [carbon monoxide (CO) and cyanide], and organic solvents. The primary questions that must be addressed relate to the mechanism(s) and the exposure conditions under which these chemicals potentiate temporary and permanent hearing impairments under permissible noise exposure conditions. This focus can provide insights into the nature of the interaction and will provide opportunities for selective pharmacological treatments designed to protect workers. In addition to characterising the doses that lead to potentiation of NIHL and evaluating the equal energy principle when a chemical toxicant is present, it must also be determined how the noise spectrum influences the nature of the interaction with chemical asphyxiants.

The nature of potentiation

Interactions among multiple chemicals presented

as a mixture is an area of intense concern recognised as a priority research area by NIOSH (cf. USDHHS, 1996), the EPA (USEPA, 1986), the National Institute for Environmental Health Sciences, WHO, and other organisations concerned with real world toxic processes. Interactions may reflect toxicokinetic processes of chemical uptake, distribution, and excretion that are altered by one of the agents resulting in a different dose of the second agent reaching the target of interest. Noise, for example, might alter distribution of agents to the cochlea by altering cochlear bloodflow or metabolic substrate utilisation or it might disrupt the cochlear-blood barrier permitting more of the toxicant to enter the cochlear compartment. Interactions between agents may also occur due to synergy between the mechanisms of toxicity. While terminology varies from source to source, there is a finite number of interactions that can occur between and among agents. Agents may have an additive effect in which the effect of simultaneous exposure to two (or more) agents reflects the arithmetic sum of their individual effects. Agents may also have a synergistic or potentiating effect in which case the outcome of combined treatment is significantly greater than the arithmetic sum of the individual effects. In experiments published by this laboratory (e.g. Young et al., 1987; Fechter et al., 1988; Fechter, 1989), profound potentiation of NIHL by CO was readily identifiable as a broad hearing loss reaching a magnitude of 60 dB loss at the highest tone frequencies, while noise alone produced NIHL of 20 dB or less and CO produced no threshold shift. The magnitude of hair cell loss is likewise substantially greater than the sum of the effect of the individual agents, noise and CO.

Chemical asphyxiants as ototoxicants

Hypoxia, ischaemia, CO exposure, and cyanide can all impair aspects of cochlear function although the studies that are reported have generally been designed to assess acute and/ or high dose effects. In addition, the disruption of blood supply (ischaemia) and reduction in available oxygen levels have been suggested to be fundamental mechanisms that are responsible for many forms of sudden hearing loss and drug ototoxicity (Hawkins, 1967; Lawrence, 1970; Thorne and Nuttall, 1987). Reduction of inhaled oxygen to 16% (via N2 dilution of air) resulted in a loss in endocochlear potential (EP) and of cochlear oxygen levels (Nuttall and Lawrence, 1980). Short duration asphyxiation (as short as 30-45 sec) results in a loss in tuning sensitivity for inner hair cells (Russell and Cowley, 1983; Brown et al., 1983; Nuttall, 1984). Similarly, acute CO intoxication can yield profound hearing loss in humans (Sato, 1966; Morris, 1969; Goto et al., 1972; Makishima et al., 1977). Seidman and colleagues (1991) have published data suggesting that free oxygen radical generation results from ischaemia and is responsible for such ototoxicity. This laboratory (Liu and Fechter, 1995; Fechter et al., 1997) has also found evidence for excitotoxicity and free oxygen radical generation in subjects exposed to CO (see below).

Cyanide may also represent a source of hearing loss though it has received less attention than hypoxia and CO. van Heijst et al. (1994) studied 20 patients in Tanzania with sudden onset polyneuropathies that included hearing loss in 9 cases, of which 3 were especially severe. Blood cyanide and plasma thiocyanate levels were significantly elevated with the source believed to be increased dietary intake of cassava due to food shortages. Direct experimental evidence that cyanide can produce hearing loss is limited to one study. Konishi and Kelsey (1968) demonstrated the loss of cochlear potentials when a solution of sodium cyanide (50mM) in artificial perilymph was perfused through the guinea pig cochlea.

Carbon monoxide: temporary threshold shifts, free radical generation, and excitotoxicity

Acute high dose CO exposure resulting from

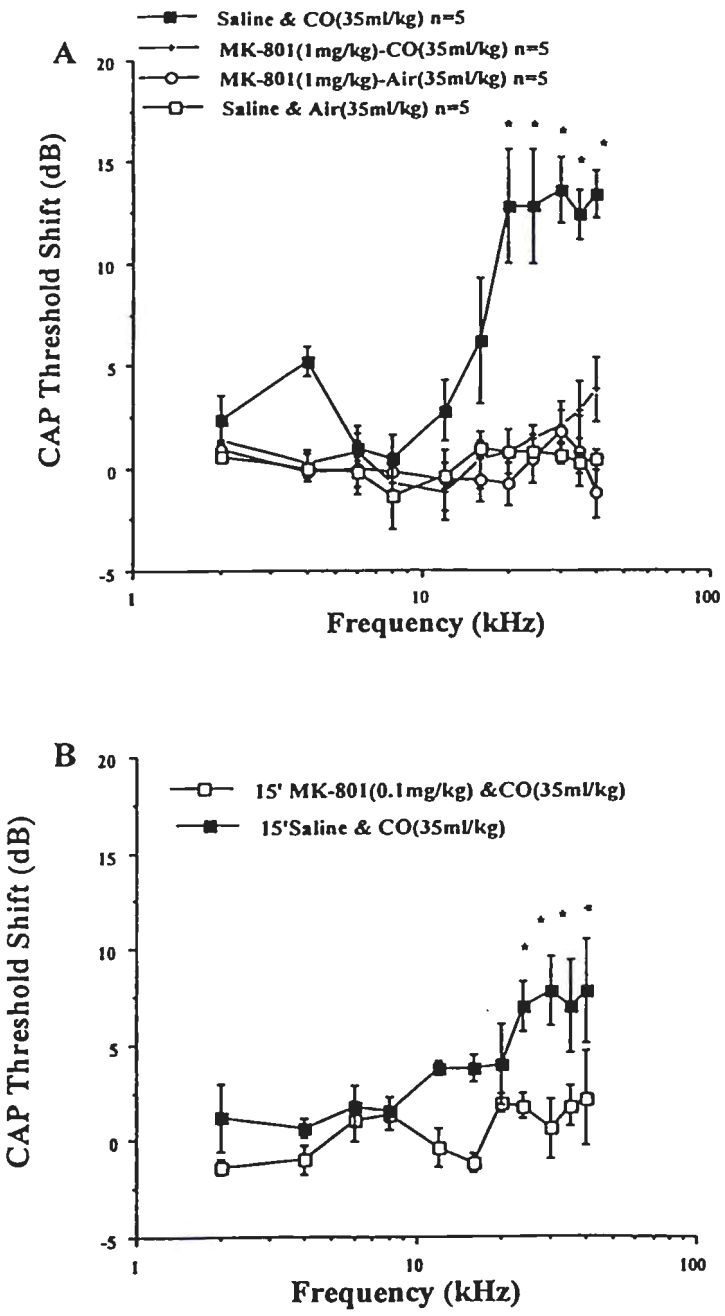

Figure 1 (A and B). Shift in compound action potential threshold sensitivity (mean ± SE) in guinea pigs receiving MK-801 (1 mg/kg) or saline 15 min prior to carbon monoxide injection. A significant loss in threshold sensitivity occurred in the CO and saline group compared to all other treatments [$F_{(3,16)} = 37.2$, $p < 0.001$]. MK-801 (1 mg/kg ip) was effective in preventing a CO-induced loss of threshold sensitivity measured 30 min following CO and had no effect on hearing given by itself ($p > 0.05$). MK-801 (0.1 mg/kg) provides protection 15 min after CO injection ($F = 17.7$, $p < 0.001$). This protection was not apparent 30 or 60 min after CO exposure between the groups. *$p < 0.05$.

direct administration of the gas intraperitoneally produces a rapid dose dependent elevation of carboxyhaemoglobin (COHb) levels that remains stable for about 1 hr before recovering (Fechter et al., 1987; Liu and Fechter, 1995; Fechter et al., 1997). This route of administration permits longitudinal within-subject measurement of cochlear impairment and recovery resulting from CO administration. Fechter et al. (1987) demonstrated in rats and Fechter et al. (1997) confirmed in guinea pigs that acute CO exposure raises preferentially the sound energy necessary to elicit the CAP for high frequency sound. In fact, the loss in cochlear sensitivity over time and its recovery follows a strict tonotopic relationship with the highest frequencies showing the earliest loss and slowest recovery (Fechter et al. 1987). In contrast to this finding, the CM amplitude measured from the round window, a non-propagated ac potential, generated predominantly by the outer hair cell (Cheatham and Dallos, 1982; Trautwein et al., 1996) is only slightly disrupted by CO administration. Based upon the selective pattern of CAP threshold shift and only a mild shift in the CM amplitude, CO appears to disrupt the primary sensory receptor cells (the inner hair cells), the post-synaptic Type 1 spiral ganglion cells, and/or the synaptic junction between these cells. The CAP reflects auditory sensitivity to sound as it is the propagated output of the cochlea generated at the spiral ganglion cell.

Pharmacological treatments can block the impairment of CAP threshold by CO suggesting likely mechanisms by which toxicity occurs. Administration of MK-801 (0.1-1.0 mg/kg) is able to block the elevation in auditory thresholds by CO observed 15 min (0.1 mg/kg MK801) or 15-60 min (1.0 mg/kg MK801) after CO exposure (see Figure 1A and B). MK-801 has also been shown to be neuroprotective in the brain to hypoxic/ischaemic insult and is believed to function by moderating the effects of excessive glutamate neurotransmitter release through blockade of the NMDA receptor (e.g. Steinberg et al., 1995; Hagberg et al., 1994; Tymianski et al., 1994). However, MK-801 also produces hypothermia when given systemically and such effects are known to reduce CO toxicity in the brain. Hypothermia can also depress electrophysiological potentials (although we do monitor the subject's core temperature and maintain it at 39° C). Therefore, Liu and Fechter (1995) employed topical administration of MK-801 (1mM for 15 min) to the semi-permeable round window of the cochlea and demonstrated that this treatment could also block the ototoxic effects of CO administration, for at least 60 min following CO administration, making the "non-specific" systemic effects of the drug an unlikely explanation for protection (see Figure 2A, B, C).

The synthesis of several free radicals including superoxide (Lafon-Cazal, 1993), hydroxyl radical (Halliwell and Gutteridge, 1985), and nitric oxide (Bredt et al., 1991; Bredt and Snyder, 1992) may be related to NMDA receptor activity. The role of free radicals in cell degeneration induced by activation of excitatory amino acid receptors was initially reported by Dykens et al. (1987) who showed that cerebellar neuron damage induced by kainate could be attenuated by superoxide dismutase, allopurinol, and hydroxyl radical scavengers. Further investigations support the linking of free radicals to excitotoxicity (Lafon-Cazal et al., 1993; Coyle and Puttfarcken, 1993). Lafon-Cazal et al. (1993) reported that superoxide is likely to be the primary neurotoxic free radical leading to a cascade of events responsible for the final cerebellar granule cell death induced by NMDA. This suggests that excitotoxicity and oxidative stress may be sequential and interactive mechanisms leading to neuronal degeneration (Coyle and Puttfarcken, 1993). Based upon these findings, an experiment was designed to assess whether free oxygen radical generation might play a role in CO ototoxicity.

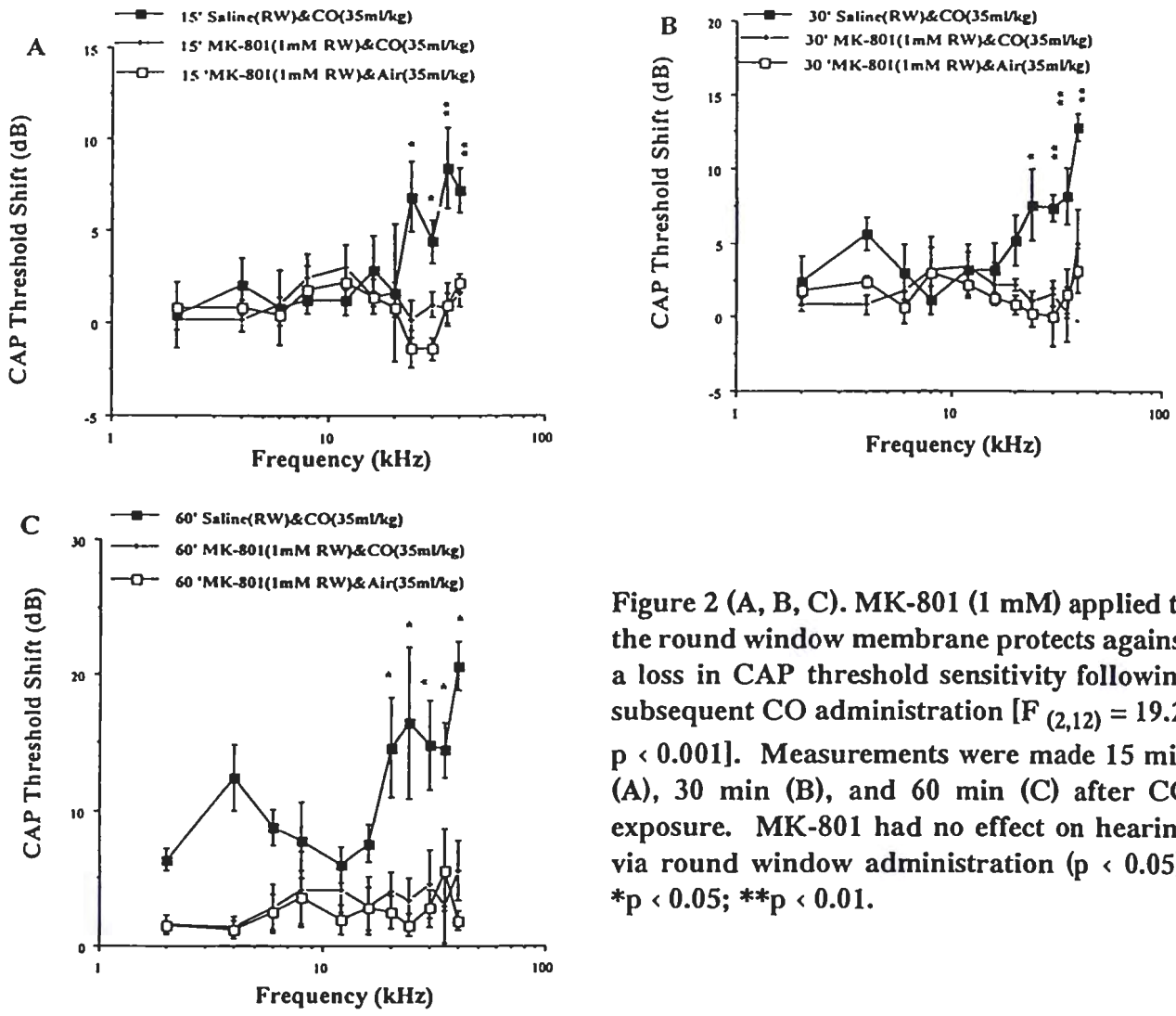

Figure 2 (A, B, C). MK-801 (1 mM) applied to the round window membrane protects against a loss in CAP threshold sensitivity following subsequent CO administration [$F_{(2,12)} = 19.2$, $p < 0.001$]. Measurements were made 15 min (A), 30 min (B), and 60 min (C) after CO exposure. MK-801 had no effect on hearing via round window administration ($p < 0.05$). *$p < 0.05$; **$p < 0.01$.

In these experiments, guinea pigs were pretreated with the free oxygen radical scavenger, phenyl-n-tert-butylnitrone (PBN 100 mg/kg ip) or saline 60 min prior to injection of CO gas ip or air. Auditory thresholds and CM amplitude were monitored prior to PBN or saline and 60 min following injection (i.e. just before CO or air administration). Thresholds and CM amplitude were also measured at 15, 30 and 60 min after CO exposure. There were no significant shifts in CAP threshold or CM that could be attributed to PBN or saline treatment. Subjects treated with saline and CO showed the characteristic elevation in CAP threshold for high frequency tones (16-40 kHz) that we have reported earlier at 60 min following gas administration (see Figure 3). However, the loss of CAP sensitivity was prevented by PBN treatment (see fig 3). PBN treatment by itself did not disrupt threshold sensitivity (see Figure 3). Comparable outcomes were obtained in a follow-up experiment utilising allopurinol (100 mg/kg ip) rather than PBN. Allopurinol acts as a free radical inhibitor specific to the xanthine oxidase pathway. Once again subjects treated with vehicle and CO demonstrated a marked loss in high frequency threshold sensitivity. This loss was blocked by allopurinol treatment given prior to the CO administration (see Figure 4).

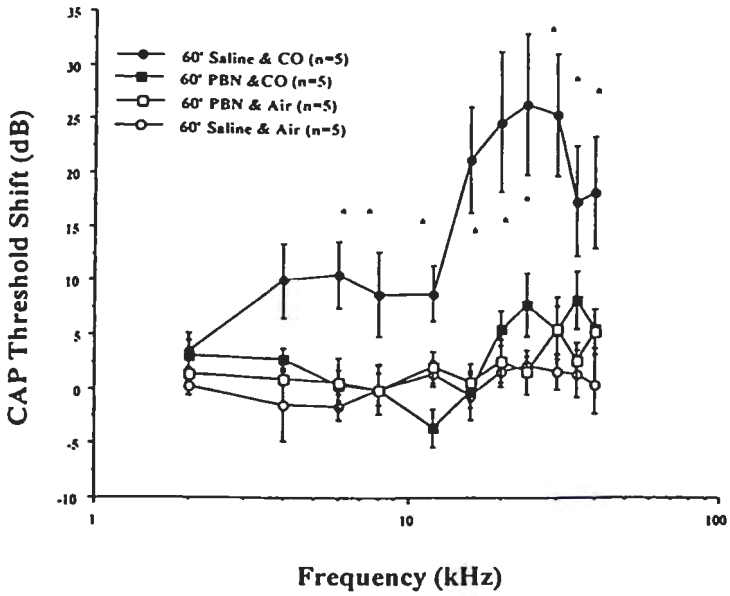

Figure 3. Shift in compound action potential threshold for guinea pigs pretreated with PBN (100 mg/kg) and saline and then administered carbon monoxide and air 60 min later. Loss of threshold sensitivity occurs at high frequencies in subjects receiving saline followed by carbon monoxide. The disruption of auditory threshold sensitivity by carbon monoxide is blocked by PBN. Values presented are means ± SE. A significant frequency x treatment interaction ($F = 5.110$; $p < .0001$) was found along with a significant treatment effect ($F = 14.044$; $p < .0001$). Sheffe's analysis showed a significant difference between the saline-CO group and all other groups ($p < .0002$).

Carbon monoxide potentiates NIHL

While CO given alone produces a transient hearing impairment, CO exposure can potentiate NIHL in rats (Young et al., 1987; Fechter et al., 1988; Fechter, 1989) producing permanent functional impairments and corresponding histopathological injury. Simultaneous noise and CO exposure result in profound auditory impairments while subjects treated with CO alone and tested 4-8 weeks later show no such impairment. Only minor shifts in threshold and discrete hair cell lesions were observed in subjects receiving noise only. Subjects were matched for auditory thresholds behaviourally over 1-2 weeks (depending upon number of thresholds tested). Different groups of rats were then exposed to broad band noise alone, CO alone, noise + CO, or placement in exposure chambers with air and no added noise. The noise exposure consisted of a 105 dBA (Fechter et al., 1988, Fechter, 1989) and 110 dBA (Young et al., 1987) broad band noise having peak intensity between 4 and 8 kHz. Exposure was for a period of 2 hr. Most of the experiments used inhalation exposures of 1200 ppm CO although lower concentrations (250 and 500 ppm) were included in one study (Fechter, 1989). Exposure to CO was for a period of 210 min. In subjects exposed simultaneously to noise and CO, this allowed for a period of CO exposure of 90 min prior to adding the 2 hr of noise. The rationale for this was to permit COHb levels to approach a steady state prior to adding noise. Auditory thresholds were reassessed 1-8 weeks following exposure depending upon the study and histological sections were prepared in one study (Fechter et al., 1988) to assess damage to the organ of Corti. Because the behavioural test method required repeated testing over several days, it was not possible to determine whether the exposures produces TTS.

Subjects exposed to 105 dBA noise + 1200 ppm CO showed a statistically significant loss in auditory sensitivity from pre-exposure levels ranging from 20-60 dB; those exposed to noise alone showed auditory threshold shifts that were less than 20 dB and were present at only a limited number of test frequencies. Neither the subjects receiving CO alone nor untreated

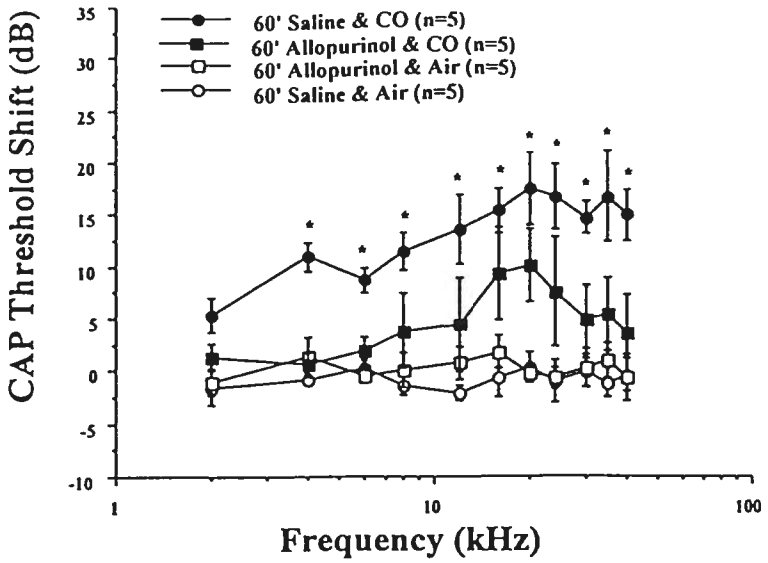

Figure 4. Shift in compound action potential threshold for guinea pigs pretreated with allopurinol (100 mg/kg) and saline and then administered carbon monoxide and air. Loss of threshold sensitivity occurs at high frequencies in subjects receiving saline followed by carbon monoxide observed 60 min following carbon monoxide. The disruption of auditory threshold sensitivity by carbon monoxide is blocked by allopurinol administered prior to carbon monoxide exposure. Values presented are means ± SE. A significant frequency x treatment interaction ($F = 38.355$; $p < .02$) was found along with a significant treatment effect ($F = 14.044$; $p < .0001$). Sheffe's analysis showed a significant difference between the saline-CO group and all other groups ($p < .0001$).

controls showed a significant loss in threshold sensitivity. Assessment of inner and outer hair cell injury measured 8 weeks following exposure demonstrated that noise exposure produced limited injury to the outer hair cells of the basal turn; combined noise + CO yielded a loss of outer hair cells that extended over the basal 50% of the cochlea. Inner hair cell damage in these subjects was marked in the basal most 15% of the cochlea. Subjects receiving CO treatment alone and untreated controls showed no loss of hair cells. Spiral ganglion cell loss was not assessed in this study.

In a subsequent study (Fechter, 1989) that used comparable noise conditions, CO exposures of 500 ppm or greater did yield significant potentiation while exposure to 250 ppm CO + noise did not produce a permanent threshold shift at 10 and 40 kHz. Impairments were somewhat greater at 40 kHz than at 10 kHz. While these levels of CO exposure are substantially higher than OSHA PEL levels, they do represent realistic levels experienced in fires and levels that may be achieved under accidental exposure conditions. They also reflect permanent outcomes of fairly short duration exposures (2 hr) to broad band noise.

Previous studies demonstrate (Young et al., 1987; Fechter et al., 1988; Fechter, 1989) that CO can potentiate NIHL under specific conditions, but the exposure parameters that enhance risk of NIHL were not identified. High concentrations of CO alone can produce temporary threshold shifts (TTS) through a

process that entails the generation of free oxygen radicals and excess release of the excitatory neurotransmitter, glutamate (Liu and Fechter, 1995; Fechter et al., 1997). Free radical generation has also been identified as a mechanism of ototoxicity related to organotins (Clerici, 1995), aminoglycoside antibiotics (Garetz et al., 1994; Priuska and Schacht, 1995) and cisplatin (Rybak et al., 1995; Ravi et al., 1995). It may also play a substantive role in some forms of noise induced hearing loss (Seidman et al., 1993; Quirk et al., 1994; Jacono et al., 1998).

Solvents as ototoxicants

Chronic low level occupational solvent exposure as well as high dose self-administration of solvents can produce hearing loss in humans. This fact has not received sufficient attention largely because solvent exposure in the workplace commonly occurs in the presence of noise, which is the archetypical environmental source of hearing loss. Morata et al. (1994), using the NIOSH National Occupational Exposure Survey, estimate that approximately 5 million American workers are exposed to organic solvents that produce ototoxicity in humans. The overwhelming majority of these individuals are also exposed to noise. Approximately 2 million of these individuals are exposed to toluene while roughly 400,000 are exposed to trichloroethylene (TCE). Hearing loss under these circumstances is typically attributed to the noise. However, solvents not only produce hearing loss directly in humans, but can also enhance the disruptive effects of noise on hearing (cf. Rybak, 1992; Johnson and Nylen, 1995 and literature cited below). In addition to occupational exposure, solvent use is ubiquitous.

Permissible exposure levels (PELs) for toluene, TCE, and noise and biomarkers of solvent exposure

Toluene is produced in quantities of 2.8 million metric tons per year in the US (USITC, 1993) and it is a significant constituent in glues and paints and is ubiquitous in hazardous waste sites. The PEL for toluene is 100 ppm (1989) and the neuro/psychological effects of exposure constitute a prominent adverse effect recognised in threshold setting. Production of TCE in the US is in the hundreds of million pounds per year, (USDHHS, ATSDR, 1997). TCE has been used in dry cleaning, in typing correction fluid, and as a degreaser; consequently, large numbers of individuals were exposed to at least low doses of this agent. Its predominant use remains degreasing of metal parts. It is also a significant contaminant at hazardous waste sites.

OSHA has set PELs for both toluene (OSHA 1989) and for TCE (OSHA, 1993) at 100 ppm over an 8 hour workday. Humans exposed to 80ppm toluene for 4 hr show a steady state blood concentration of 6-7μM toluene (Hjelm et al., 1988; Lof et al., 1990). It is anticipated, based upon laboratory studies in animals as well as human autopsy, that the brain would have toluene levels between 2 (Benignus et al., 1981; Takeichi et al., 1986) and 10 (Paterson and Sarvesvaran, 1983) times higher than blood levels - a finding consistent with the brain's high lipid content and known susceptibility to acute toxicity. Thus exposure to toluene at levels below threshold limit values can be predicted to yield toluene levels in brain of 12-70 μM.

While the metabolism of TCE complicates assessment of blood concentrations that correspond to inhalation exposures, 50 ppm exposure for 4 hr produces human blood concentrations of 6μM (Sato et al., 1991) while exposure at the PEL of 100 ppm for eight hours yields blood concentrations of 13μM (Sato and Nakajima, 1978). Brain TCE levels are likely to surpass blood levels significantly.

Epidemiology of solvent-induced hearing loss

Epidemiological studies demonstrate direct

solvent-induced hearing loss and noise induced hearing loss enhanced by solvents. Morata et al. (1993) studied 190 workers from printing and paint manufacturing industries in Brazil. Workplace toluene exposures were estimated at 100-365 ppm and noise levels between 88-93 dBA. Comparisons made among groups exposed to a mixture of solvents (with toluene as the predominant component), noise, noise plus solvent, and unexposed controls showed significant hearing impairments in all groups compared to control. The odds ratio for hearing impairments was approximately 4 for the noise exposed group, 5 for the mixed solvent group, and nearly 11 for subjects receiving combined exposure to noise and solvents. While these toluene exposure levels were high compared to US PEL values, Abbate et al. (1993) observed significantly elevated latency in the brainstem auditory evoked potential among normal hearing workers exposed to toluene for 12-14 years at average exposure levels of 97 ppm compared to unexposed controls. The initial component of the brainstem response, wave I, indicative of cochlear function, was especially affected. These data demonstrate sub-clinical changes in auditory function in a solvent exposed population. Actual hearing loss has been reported in glue sniffers who expose themselves to high toluene doses (Ehyai and Freemon, 1983).

Morata (1989) showed an interaction between noise and carbon disulfide exposure among workers exposed to noise levels of 86-89dBA and carbon disulfide levels of approximately 30 ppm (OSHA PEL=20 ppm). Hearing loss among the exposed subjects was extremely high ranging from approximately 45% for those exposed for 0-2 years to 70% among workers exposed for 6 years or longer. These rates of loss are far higher than would be predicted from noise exposures of these intensities although baseline levels of noise induced hearing loss among workers not receiving carbon disulfide are unavailable.

Szulck-Kuberska et al. (1976) demonstrated loss in auditory sensitivity among 26 out of a total of 40 workers studied who were exposed to TCE. Auditory impairments were more common among workers exposed to TCE for a longer duration.

Muijser et al. (1988) reported hearing loss among workers exposed to styrene in the plastics industry, compared to one of two control groups. Jacobsen et al. (1993) showed significantly elevated hearing impairments in workers exposed to mixed organic solvents (not specified but including solvents used in degreasing operations and painting) for a period of five years or more as compared to unexposed controls (N=3,284). Bergstrom and Nystrom (1986) also reported elevated rates of hearing impairment in an epidemiological study of workers (N=319) in the paper mill industry exposed to industrial solvents (not specified) despite the fact that noise exposures were relatively low (80-90dBA).

Solvents as ototoxicants: *in vivo* laboratory studies

Organic solvents represent a very interesting, yet confusing group of ototoxic chemicals. First, they appear to preferentially impair auditory function for sounds of mid frequency (Crofton, 1994) rather than the high frequencies that are so much more commonly the targets of ototoxicants. Secondly, despite this shared functional impairment, organic solvents may actually target different cell types and produce their effects by multiple mechanisms. Clearly, such a diversity of mechanisms, if true, presents significant challenges in developing therapeutic strategies for reversing or blocking auditory impairment! The following review focuses on two ototoxic solvents, toluene and trichloroethylene, which underscore the above comments.

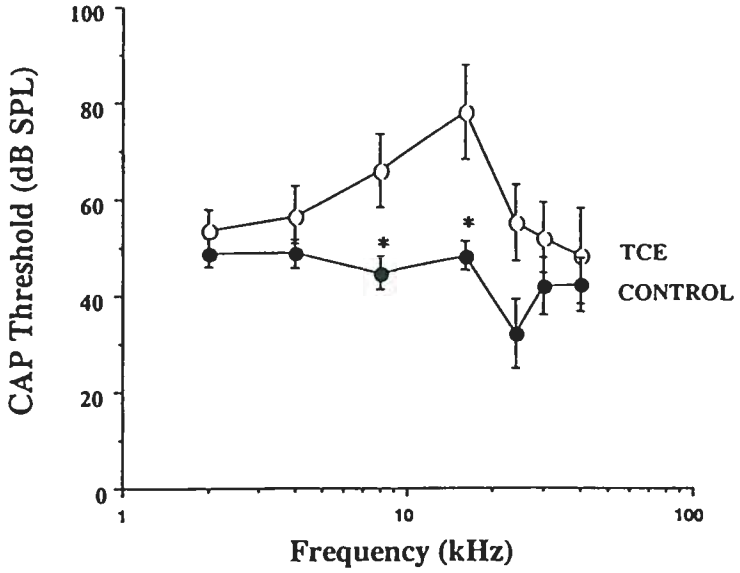

Figure 5. Trichloroethylene exposure produced a permanent mid-frequency hearing loss in rats as evidenced by elevation in sound level necessary to elicit a CAP. Animals tested 4 to 5 weeks after exposure to air only (AIR) or 4000 ppm trichloroethylene (TCE) 6 h/day for 5 consecutive days. Data are presented as group means (± SE) (*Significantly different from controls, $p < 0.05$; n = 10/group).

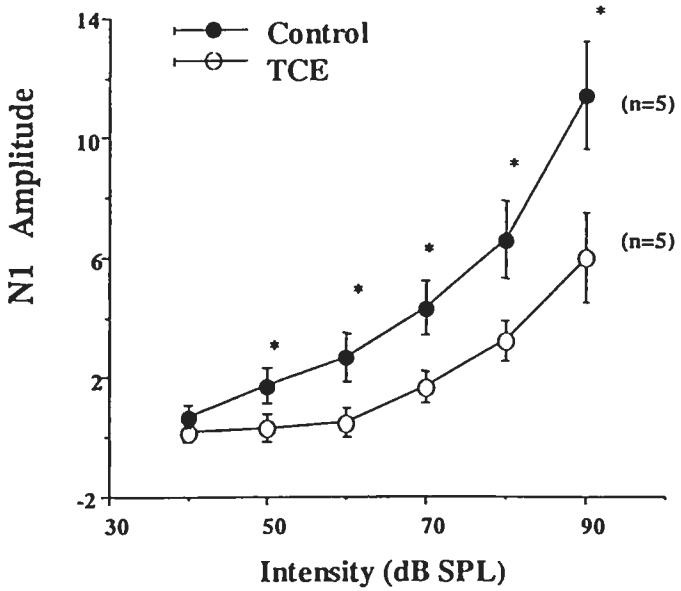

Figure 6. Growth of the CAP amplitude in response to increasing sound levels at 16 kHz for rats exposed to air only (AIR) or 4000 ppm trichlorothylene (TCE) 6 h/day for 5 consecutive days and tested 4-5 weeks after exposure. TCE subjects showed a depressed CAP amplitude at sound levels from 50 to 90dB SPL. Data are presented as group means (± SE) (*Significantly different from controls. $p < 0.05$; n = 10/group).

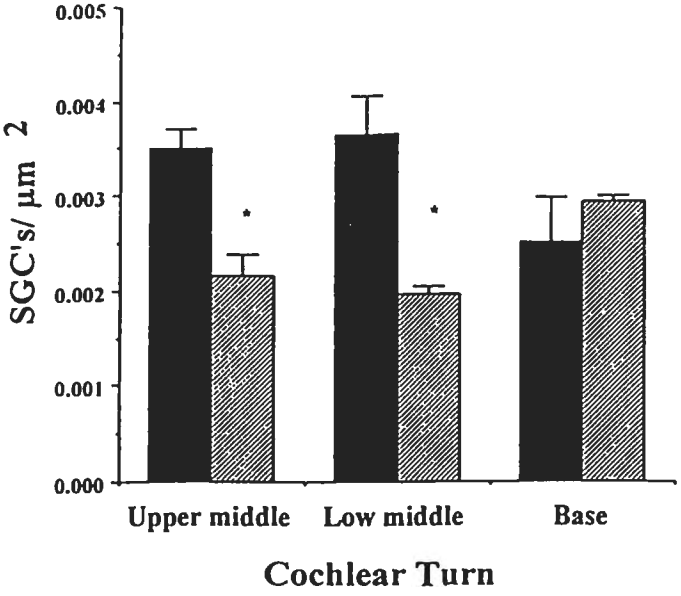

Figure 7. TCE decreases the density of spiral ganglion cells in the lower-middle and upper-middle turns of the cochlea. Rats were exposed to air or 4000 ppm TCE 6 hr/day for 5 consecutive days and were euthanized 10 weeks following exposure. Data are presented as group means (± SE) (*Significantly different from controls, $p < 0.05$; n = 4/group).

Trichloroethylene

Crofton and Zhao (1993) reported a selective permanent impairment in auditory thresholds at middle frequencies in animals exposed to 4000ppm TCE for 8 hr/day for 5 days. More recent studies have replicated these behavioural findings and provided both electrophysiological and histological findings that facilitate identification of a likely target for this ototoxicant. Fechter et al. (1998) conducted parallel behavioural and electrophysiological studies in rats exposed to TCE as described by Crofton and Zhao (1993). Not only were behaviourally determined thresholds for middle frequencies elevated, but CAP thresholds were also elevated for these same tones (see fig 5). When sound levels above threshold were evaluated for a mid frequency tone, SGC output (N1 amplitude) was at lower voltages among TCE treated subjects than controls indicating a loss of responsive units (fig 6). Light microscopy conducted in the lab confirmed a loss of SGCs in TCE-treated subjects that seems consistent with the pattern of preferential middle frequency loss (see fig 7). CM, generated predominantly by OHCs, was not reduced as compared to control subjects (data not shown) thus demonstrating that SGCs were more vulnerable than OHCs to this toxicant. These data differ from those seen with toluene where other investigators suggest that the OHC is the primary site of injury (see below). Yet, both toluene and TCE produce a preferential mid-frequency hearing impairment *in vivo*.

Toluene

In vivo laboratory studies of toluene ototoxicity have used concentrations that appear high relative to human PEL's, but in vitro investigations using cochlear cells identify specific toxic effects at concentrations that would be predicted in neural tissue during human workplace exposures within the permissible range. Rats exposed to toluene in the range of 1000-2000 ppm over 3-5 days (8-16 hr/day) develop permanent auditory impairments as reflected by the disruption of the early (cochlear) components of the auditory brainstem response (ABR) or by behavioural testing (e.g. Rebert et al., 1983; Johnson, 1994; Crofton et al., 1984; Pryor et al., 1984; Sullivan et al., 1988), but it is unknown whether temporary, acute threshold shifts also occur during toluene intoxication. Sullivan et al. (1988) and Johnson

and Canlon (1994) published histological data that demonstrate OHC damage especially at middle turns of the cochlea following toluene exposure. Johnson and Canlon showed (1400ppm, 16 hr/day for 3-8 days) functional impairment (DPOAE) that also supports a significant OHC involvement. It is not known whether the IHC and/or SGC might also be a target for toluene, whether there is a difference in susceptibility of these different cell types to toluene, and how toluene impairs cochlear cells. While the bases by which solvents impair cochlear function are unclear, recently published in vitro findings suggest that at least one of these agents, toluene, disrupts outer hair cell length and intracellular calcium homeostasis. It is not certain that these processes underlie cochlear impairment, but they do provide initial clues that may relate to this issue.

Toluene disrupts OHC motility *in vitro* preferentially for cells from middle apical end of cochlea

Toluene 100μM promotes significant reductions in OHC length especially from long OHCs isolated from the apical-middle half of the cochlea responsible for low-mid frequency hearing than from the basal or high frequency half of the cochlea (see Figure 8). This finding suggests that intrinsic cell characteristics may be critical to the preferential vulnerability of the cochlea to mid frequency hearing loss for toluene. By contrast, trimethyltin (100 mg/mg) which impairs high frequency hearing did not produce this pattern of loss (Figure 9) indicating that cells from the apical half of the cochlea when studied in primary culture are not more susceptible to impairment due to culture conditions or superfusion with ototoxicants in general.

Toluene elevates $[Ca_i^{2+}]$ in OHCs and SGCs by disrupting storage of Ca^{2+} from intracellular stores

Toluene (30μM-100μM) causes a significant elevation of $[Ca_i^{2+}]$ in both OHCs and SGCs (Figure 10) as indicated by the ratiometric calcium indicator, FURA 2. $[Ca_i^{2+}]$ starts to increase about 2 min after exposure to toluene and shows partial or full recovery depending upon concentration (data not shown).

Because of concern about the specificity of the increase in $[Ca_i^{2+}]$ produced by toluene at doses of 30μM, control studies were conducted in which benzene was added to artificial perilymph following the same procedures outlined above for toluene. Disruption in OHC $[Ca_i^{2+}]$ occurred only at benzene concentrations of 1 mM (highest concentration tested) suggesting that OHC $[Ca_i^{2+}]$ homeostasis is not especially sensitive to this agent. This finding is important because benzene does not produce ototoxicity (Pryor, 1995). Toluene increases $[Ca_i^{2+}]$ even after removing Ca^{2+} from the extracellular environment suggesting that the elevation of $[Ca_i^{2+}]$ is from intracellular sources (see Figure 11). The preferential treatment in $[Ca_i^{2+}]$ in OHCs over SGCs, the transient response observed at low concentrations, and the apparent independence from extracellular Ca^{2+} seen with toluene can be differentiated from the effects seen using TMT. TMT preferentially affects SGCs over OHCs has permanent effects, and entails an extracellular as well as intracellular source for elevation in $[Ca_i^{2+}]$ levels.

$[Ca_i^{2+}]$ homeostasis is controlled at the plasma membrane by membrane-associated Ca^{2+} transport systems, and by intracellular compartmentalisation of Ca^{2+} (Carafoli, 1987). Plasma membrane Ca^{2+} transport is dependent, in turn, upon three primary factors: uptake via Ca^{2+} channels, uptake via a Na^+/Ca^{2+} exchanger and extrusion of Ca^{2+} from the cell - a process that is dependent upon a specific ATPase. Activation of Ca^{2+} channels and the Na^+/Ca^{2+} exchanger

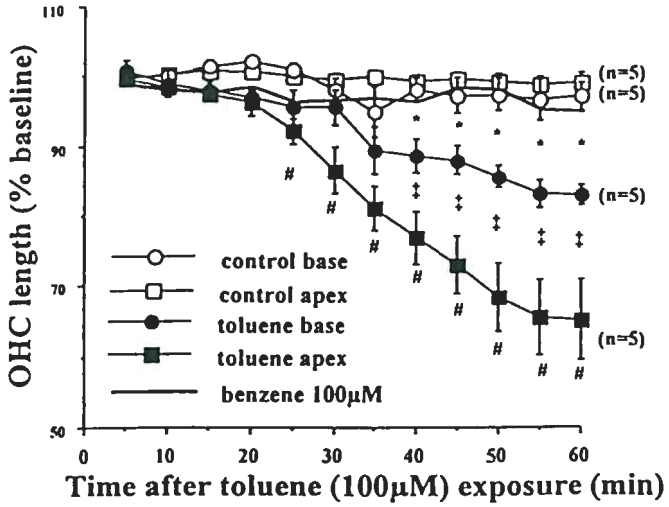

Figure 8. Effect of 100 μM toluene on length of outer hair cells isolated from apical and basal portions of the cochlea and maintained in artificial perilymph. *Significant difference between toluene base and control. #Significant difference between toluene apex and control. ‡Significant difference between toluene base and toluene apex. All P values ‹ 0.003. Benzene, which is not ototoxic, served as a control for non-specific solvent effects. *Reprinted from Hearing Research, Vol. 112 Liu et al., "Correspondence between middle frequency auditory loss in vivo and outer hair cell shortening in vitro," pp 134-140, 1997, with kind permission of Elsevier Science - NL, Sara Burgerhartstraat 25, 1055 KV Amsterdam, The Netherlands.*

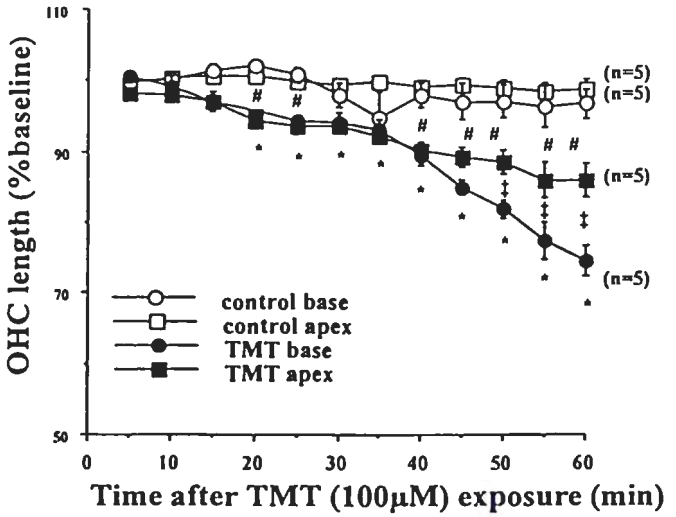

Figure 9. Effect of 100 μM TMT on length of outer hair cells isolated from apical and basal portions of the cochlea and maintained in artificial perilymph. *Significant difference between TMT base and control. #Significant difference between TMT apex and control. ‡Significant difference between TMT base and TMT apex. All P values ‹ 0.005. *Reprinted from Hearing Research, Vol. 112 Liu et al., "Correspondence between middle frequency auditory loss in vivo and outer hair cell shortening in vitro," pp 134-140, 1997, with kind permission of Elsevier Science - NL, Sara Burgerhartstraat 25, 1055 KV Amsterdam, The Netherlands.*

provide the inward directed flux of Ca^{2+}. The specific ATPase, on the other hand, exports Ca^{2+} from the cell in order to maintain the low level [Cai^{2+}] necessary to maintain the health of the cell (Caroni and Carafoli, 1981). The intracellular compartmentalisation system for Ca^{2+} regulation includes uptake and release of Ca^{2+} from intracellular Ca^{2+} stores such as mitochondria and the endoplasmic reticulum.

Electron probe X-ray microanalysis has also shown the endoplasmic reticulum is a major intracellular store of Ca^{2+} (Somlyo et al., 1985). Its Ca^{2+} regulation may be through an ATPase, calmodulin (Moore and Kraus-Friedmann, 1983, Famulski and Carafoli, 1984). The mitochondrion has the capacity to sequester

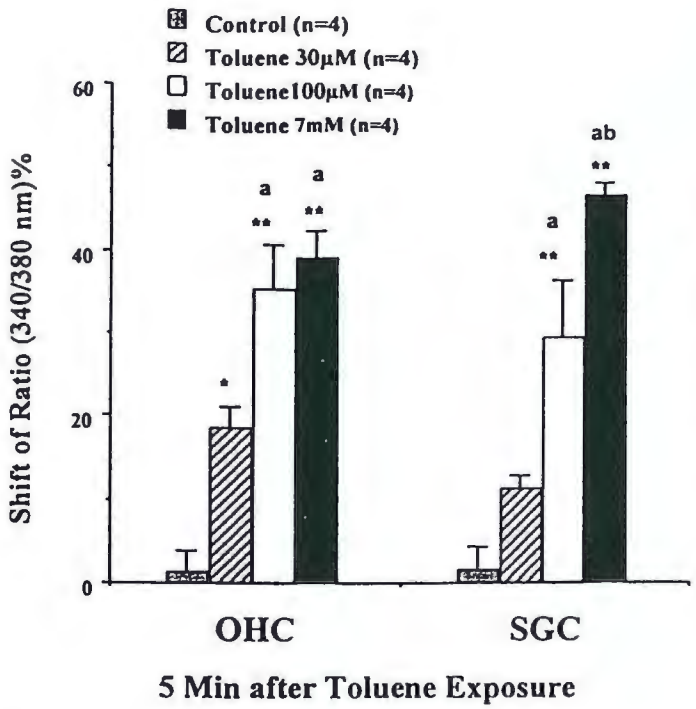

Figure 10. Effect of toluene on fluorescence ratios at 340/380 nm in outer hair cells and spiral ganglion cells showing a dose-dependent increase in [Ca2+]i 5 min following toluene administration as a function of toluene concentration in perilymph. Values plotted represent means ± SE. *Significant difference between treatment group and control ($p < 0.05$). **Significant difference between treatment group and control ($p < 0.01$). [a]Significant difference between treatment group and 30 μM group ($p < 0.01$). [b]Significant difference between treatment group and 100 μM group ($p < 0.05$).

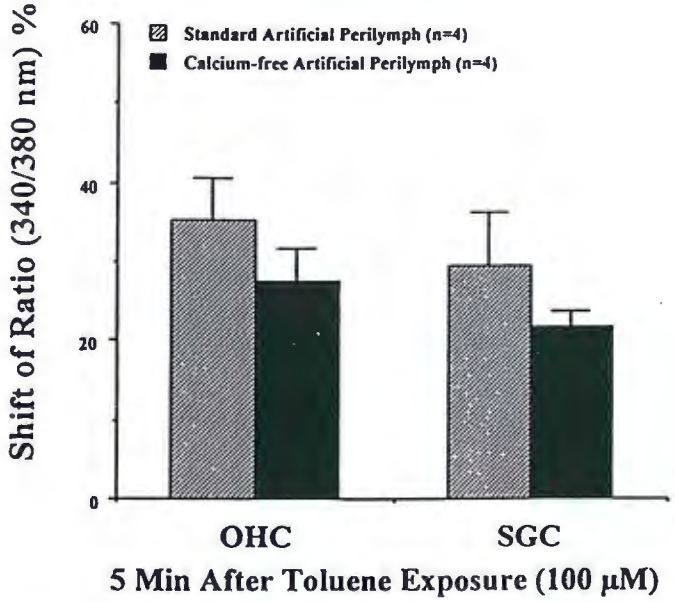

Figure 11. Effect of toluene on fluorescence ratios at 340/380 nm in outer hair cells and spiral ganglion cells maintained in normal artificial perilymph or nominally calcium-free artificial perilymph. Values plotted represent means ± SE Toluene elevates $[Ca2+]_i$ to equivalent levels regardless of the calcium content of the artificial perilymph.

large quantities of Ca^{2+} and act as efficient buffers of $[Cai^{2+}]$ under toxic conditions although it contains low Ca^{2+} concentration under physiological conditions (Somlyo et al., 1985; Orrenius et al., 1992). The driving force for the continuous Ca^{2+} pumping is provided by the transmembrane potential. The nucleus also has high Ca^{2+} buffering capacity and is involved in the regulation of $[Cai^{2+}]$ (Nicotera et al., 1990a, 1990b).

The data showing that elevation of $[Cai^{2+}]$ by toluene still occurs when Ca^{2+} is absent in the extracellular buffer suggests that the influx of

Ca^{2+} through the plasma membrane may not be an important source of elevation of $[Cai^{2+}]$ in outer hair cells and SGC exposed to toluene. On the other hand, according to our data, at least two pathways of elevation of $[Cai^{2+}]$ in toluene ototoxicity may be involved. First, the intracellular Ca^{2+} -sequestering system may not take up or release Ca^{2+} properly. Additionally, the intracellular Ca^{2+} exclusion system may not operate effectively. It is of interest that we have identified a disruption of $[Cai^{2+}]$ among both spiral ganglion cells and outer hair cells exposed to toluene. The issue of whether toluene disrupts spiral ganglion cells has not been addressed in earlier in vivo studies. Therefore it is unclear whether the alterations that we see in these cells in vitro represents a non-specific toxic effect or whether it corresponds to an effect that might occur in vivo within the auditory system.

CONCLUSIONS

Chemical asphyxiants and organic solvents represent two broad classes of chemicals having direct ototoxic potential as well as the ability to interact with noise exposure yielding either additive or synergistic effects. While a free radical/excitotoxic explanation has been advanced for chemical asphyxiant impairment of cochlear function and appropriate pharmacological interventions in laboratory animals have been utilised, similar progress has not yet been realised for organic solvents. Moreover, the development of drug interventions that can be utilised safely in humans remains an ongoing challenge for pharmacology.

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