Diabetes Impairs Recovery From Noise-Induced Temporary Hearing Loss

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Objectives/Hypothesis: The purpose of this study is to investigate whether diabetes impairs the recovery from noise-induced temporary hearing loss.

Methods: Twenty-eight male Wistar rats were divided into three groups: control, diabetes with insulin control (DI), and diabetes without insulin control (DM). Diabetes was induced by intraperitoneal injection of streptozotocin. All animals were exposed to white noise at 110 dB SPL for 8 hours. Auditory brainstem response (ABR) thresholds and distortion product otoacoustic emission (DPOAE) amplitudes were measured for all animals 1 day prior to noise exposure to obtain a baseline for hearing function, and then 1 hour, 1 day, 2 days, 4 days, 7 days, and 14 days after noise exposure.

Results: One hour post exposure, ABR thresholds shifted markedly, and DPOAE was reduced similarly in all groups. Both ABR thresholds and DPOAE returned to the baseline in the control group at day 1, but they were not back to the baseline in the DM group even by day 14. Compared with the control group, the ABR threshold shifts and DPOAE returned to baseline more slowly in the DI group.

Conclusions: The present study suggests that diabetic patients need proper blood sugar control and probably need more effective preventive measures to preserve their hearing from the effects of noise.

Key Words: Diabetes, noise-induced hearing loss, temporary threshold shift, auditory brainstem response, distortion product otoacoustic emission.

INTRODUCTION

Diabetes and noise-induced hearing loss (NIHL) are both very common conditions affecting the health and quality of life.1,2 Histopathological studies of cochlea have shown damage to the nerve and vessels of the inner ear in individuals with diabetes.3 Animal studies in diabetes have also demonstrated thickening of the basement membrane in the capillaries of the stria vascularis.4 Hearing loss might represent a diabetic complication in elderly diabetic patients.5 Abnormal auditory brainstem function could be observed as early central manifestations of diabetic neuropathy.6,7

NIHL is normally associated with noise exposure in industry, and it is therefore thought of as a byproduct of modern civilization. It is mainly thought to be caused by injury to cochlear hair cells. However, as our knowledge of disorders of the auditory system increases, it has become evident that the effect of noise is complex. Exposure to a moderately loud noise causes hearing loss that decreases gradually after the end of the noise exposure.8 The hearing threshold may return to its original value after minutes, hours, or days depending on the intensity and duration of the noise exposure, as well as the individual person’s susceptibility to noise exposure. Hearing loss that resolves is known as temporary threshold shift (TTS).

Though the pathologic and animal studies suggest plausible biologic interactions between diabetes and noise, the effects of diabetes on NIHL were inconclusive in previous clinical studies. One cross-sectional study retrospectively observed a population of 229 men employed at a metal assembly plant with occupational noise exposure.9 The results suggested that diabetic workers were more prone to developing severe NIHL.9 However, in another cross-sectional study of 348 participants, diabetics demonstrated no evidence of higher permanent hearing threshold shifts than nondiabetics at the same noise levels.10
MATERIALS AND METHODS

Animals and Induction of Diabetes

Four-week-old male Wistar rats weighing 95 g to 110 g were obtained from the National Taiwan University animal center. The animals were housed in independent ventilation cages and were allowed free access to water and food. The temperature was maintained at 21±1°C, and lights were turned on from 6:30 AM to 6:30 PM. Weight and blood glucose levels of all the animals were measured weekly. The Tzuchi General Hospital Animal Care and Use Committee approved all the experimental protocols. All exposures and testing were performed during daytime hours.

The rats were fasted overnight, and diabetes was induced by a single intraperitoneal injection of 65 mg/kg of streptozotocin (STZ) in 0.1-mol citrate buffer solution (pH 4.5; Sigma-Aldrich, St. Louis, MO) at the age of 6 weeks. Blood glucose concentrations were measured in the morning via tail puncture (Glucocard Memory 2; Menarini Diagnostic, Florence, Italy) to confirm the diabetic state. Rats with blood glucose levels under 200 mg/dL at the 48th hour were excluded from the study.

Noise Exposure

All animals were individually placed in stainless steel cages. Filtered and band-passed (1–20 kHz field variation level of diabetic rats rose gradually from 100.6 to 370.1 ± 39.3 mg/dL (SE). Insulin was injected daily and subcutaneously in the DI group from the age of 10 weeks. The glucose level was reduced to 158 ± 21.7 mg/dL (SE). In general, the blood glucose level of the DM group was higher than that of the DI group; the DI group glucose level was higher than that of the control group (P<.05).

RESULTS

The blood glucose level of the control group was 105.2 ± 7.1 (SE) mg/dL. After induction of diabetes at the age of 6 weeks, the blood glucose level increased significantly in the DM and DI groups. The blood glucose level of diabetic rats rose gradually from 100.6 ± 3.9 to 370.1 ± 39.3 mg/dL (SE). Insulin was injected daily and subcutaneously in the DI group from the age of 10 weeks. The glucose level was reduced to 158 ± 21.7 mg/dL (SE). In general, the blood glucose level of the DM group was higher than that of the DI group; the DI group glucose level was higher than that of the control group (P<.05).

At the age of 18 weeks, the average body weight of the control group was 473.9 ± 4.2 (SE), the average body weight of the DI group was 398.4 ± 5.4 (SE), and the average body weight of the DM group was 301.4 ± 9.1 (SE). Throughout the experimental period, the body weight growth rates of the DM and DI groups were much lower than the control group after induction of diabetes (Fig. 1). The body weight of the DI group increased more rapidly after subcutaneous daily injection with insulin at the age of 10 weeks. These results suggest that using insulin to control blood glucose levels may enhance the growth rate of diabetic rats.

Figure 2 shows the thresholds shift of ABR in each group over time. Compared to the baseline, ABR thresholds shifted markedly after noise exposure at 1 hour in all groups (P<.05). At 1 hour after noise exposure, ABR threshold shifts were not different between groups. ABR thresholds in the control group returned to the baseline correlated with the location of the f2 frequency in the cochlea.2
at day 1 (D1). ABR in the DI group did not return to baseline at D1, a trend that was statistically different from that of the control group \((P < .05)\). In the DI group, ABR returned to the baseline at approximately D4. ABR threshold in the DM group did not return to the baseline until D14. Overall, ABR thresholds of all groups eventually returned to their original values. The recovery of TTS was mildly delayed in the DI group, and it was significantly delayed in the DM group.

Unlike the effects on ABR thresholds, diabetes and noise had different impacts on the recovery of DPOAE amplitudes. Compared to the baseline, there was a significant change for DPOAE amplitudes at a range of 4.4 kHz to 17.7 kHz in all groups immediately following noise exposure (1 h) \((P < .05)\) (Figs. 3 and 4). In the control group, DPOAE amplitudes returned to baseline at D1. DPOAE amplitudes in the DI group were different from the control group \((P < .05)\) at D1 and did not return to the baseline until D2 to D7, depending on the frequency. In the DM group, the amplitudes of DPOAE in the range of 4.4 kHz to 17.7 kHz did not return to the baseline throughout the study \((P < .05)\). As a whole, diabetes impaired the amplitude recovery of DPOAE from noise-induced injury. The presentation of DPOAE in the DI group lay between the control and the DM groups.

**DISCUSSION**

We demonstrated the chronological changes of ABR thresholds and DPOAE amplitudes after moderately loud noise exposure. Chronological ABR threshold shifts revealed that diabetes delayed the recovery from TTS. Using insulin for blood sugar control may partially prevent the delay in such recovery from noise insults. Our study results indicate that in addition to hypoxia and ischemia, reported previously, hyperglycemia might augment NIHL and attenuate the recovery from noise injury.

Early abnormalities in the micromechanical properties of outer hair cells (OHCs) could be found through otoacoustic emissions (OAEs) in subjects with insulin-dependent diabetes mellitus (IDDM). In this study, noise exposure resulted in temporary changes of DPOAE amplitudes in the C and DI groups. However, a combination of diabetes and noise exposure in the DM group...
caused marked decreases in DPOAE amplitudes from the 4.4 kHz to 17.7 kHz range, which persisted for as long as 14 days after acoustic trauma. In this study, chronological changes of DPOAE amplitudes suggested that diabetic animals exposed to moderately loud noise may develop permanent dysfunction of OHCs. The present results indicate that hyperglycemia may augment noise-induced OHC damage. This augmentation of noise-induced OHC damage has also been demonstrated by certain agents, like aminoglycosides.12

The mechanisms responsible for the stronger negative effects of diabetes on recovery from noise-induced OHC damage than on recovery from inner hair cell (IHC) damage are unknown. One possibility is the reduction of the olivocochlear efferent system. The medial olivocochlear complex (MOC) originates from neurons in medial and ventral regions of the superior olivary complex and preferentially innervates OHCs contralaterally via myelinated fibers.15 The MOC can attenuate the response of the cochlea to sound by reducing the gain of OHC electromechanical response to acoustic stimulation.15 Diabetes probably compromised this protective effect of OHCs and induced preferential damage to OHCs, as shown by better recovery of IHCs after TTS. This hypothesis warrants further investigation.

Insulin has been proved to prevent depolarization of the mitochondrial inner membrane in sensory neurons of IDDM rats in the presence of sustained hyperglycemia.16 In this study, postnoise exposure hearing levels returned to baseline faster in diabetic rats treated with insulin than in untreated diabetic rats. DPOAE amplitudes of the DI group returned to their normal values, but the amplitudes of the DM group did not. The results show that therapy with insulin can reduce diabetes-induced delay of recovery, probably through proper sugar control and by avoiding depolarization of the mitochondrial inner membrane in OHCs.

In this study, daily bolus insulin injection partially corrected the hyperglycemia. The detrimental effects of diabetes on recovery from noise-induced ABR and DPOAE changes were partially removed. Compared to intermittent injections, continuous insulin infusion (CII) in diabetes resulted in a greater reduction of glycated hemoglobin.17 However, CII is known to decrease the hormones’ metabolic effectiveness on glucose production in humans due to the body developing an increased tolerance to the hormones.18 To maintain both short-term blood glucose levels and long-term levels as well, pulsatile insulin injection offers the feasible therapy versus intermittent injections or continuous infusions. Injection of insulin in pulses simulates the physiological secretions of insulin of the pancreas. This greater efficacy of pulsatile exposure is accompanied by an equipotent effect on glucose utilization.19 However, whether complete control of hyperglycemia to the normal range and simulation of pulsatile insulin secretion may abate the detrimental effects on NIHL recovery of diabetes remains to be determined.

STZ has frequently been used to induce hyperglycemia in experimental animals through its toxic effects on pancreatic beta cells,4,20,21 thus generating diabetes in rodents pathophysiologically comparable to insulin-dependent DM in humans. This model has also been used in rodents for investigating the role of hyperglycemia in the development of diabetic inner ear pathology.4 Although hearing loss had been noted in DM induced by STZ, it was broadly believed that STZ does not induce direct damage to the inner ear. Further investigation using transgenic hyperglycemic rodents, such as the RIP-CD154 mouse model, will be warranted to confirm the findings of this study. In addition, this is the very first paper discussing diabetes effects on TTS recovery. With our findings that TTS recovery was damaged by hyperglycemia, further studies using histopathology are warranted to investigate the hair cell damages.

**CONCLUSION**

Repeated temporary threshold shifts may eventually lead to a permanent threshold shifts. This study demonstrated that ABR thresholds of noise-exposed rats can return to the baseline, but the recovery period is prolonged by diabetes. In addition, diabetes may

![Fig. 4. Comparison of shifted distortion product otoacoustic emission (DPOAE) amplitudes at (A) 4.4 kHz, (B) 8.8 kHz, and (C) 17.7 kHz between groups after noise exposure. White rhomboid = control group; black square = diabetes with insulin control (DI) group; black triangle = diabetes with insulin control (DM) group. *P < .05 (indicates a statistically significant difference from the baseline). +P < .05 (indicates a statistically significant difference from control group). #P < .05 (indicates a statistically significant difference from DI group)](image-url)
compromise the OHC function after TTS, which may leave diabetics more susceptible to hearing damage caused by loud noise. It implies that diabetic patients are potentially more susceptible to NIHL, especially with uncontrolled hyperglycemia. This study suggests that diabetic patients need proper blood sugar control and probably need more effective preventive measures to protect their hearing from noise damage.

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BIBLIOGRAPHY