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Distinction between auditory electrophysiological responses in type 1 and type 2 diabetic animal models

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HIGHLIGHTS

- We aimed to compare the auditory electrophysiological responses present in animal models of type 1 and type 2 DM.
- Hearing threshold shifts and latency delays were similar in both types of DM.
- Type 2 diabetic mice exhibited more severe damage to the central auditory pathway and the cochlear hair cells.
- These results suggest that hyperinsulinemia was associated with auditory dysfunction including central and peripheral by DM rather than hyperglycemia.

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ABSTRACT

Neurological research has focused recently on determining the molecular mechanisms of common causes of damage to the peripheral and central nervous systems. One of the metabolic systemic diseases that can result in sensorineural hearing loss is diabetic mellitus (DM). In this study, we aimed to compare the auditory electrophysiological responses present in animal models of type 1 and type 2 DM using auditory brainstem response (ABR), auditory middle latency response (AMLR), and transient evoked otoacoustic emission (TEOAE) in animal model. We found that ABR threshold shifts and latency delays were similar in both types of DM. On the other hand, we found that type 2 diabetic mice exhibited more severe dysfunction to the central auditory pathway, as measured AMLRs and the cochlear hair cells, as measured TEOAEs. These results together suggest that hyperglycemia associated with type 1 or type 2 DM causes auditory nerve dysfunction, while hyperinsulinemia associated with type 2 DM causes dysfunction to both the central auditory pathways and cochlear hair cells.

Introduction

Neurological research has focused recently on determining the molecular mechanisms of common causes of damage to the peripheral and central nervous systems. DM is both a major metabolic disease in itself and also one of the major causes of neurological diseases. The two types of DM, type 1 and type 2, are manifested by completely different mechanisms, metabolic pathologies, and characteristics [10]. Type 1 DM is caused by the loss of beta cells, and then production of endogenous insulin is severely reduced, leading to hyperglycemia and hypoinsulinemia [1]. On the other hand, type 2 DM is associated with insulin resistance or relative insulin deficiencies [6].

Hearing impairment or loss is characterized by either a partial or a total inability to hear. It is generally classified into two main types; conductive hearing loss and sensorineural hearing loss. Sensorineural hearing loss can be caused by several environmental and genetic factors, including exposure to loud noise, aging, ototoxic substances, heredity, and systemic disease [15]. One of the metabolic systemic diseases that can result in sensorineural hearing loss is DM [5]. Many studies have examined the relationship between DM and hearing impairment, but a significant correlation with DM type has not yet been described [7]. However, evidence is accumulating that DM can induce auditory functional impairment.

In our previous study, hearing impairment was observed in the streptozotocin (STZ)-induced type 1 diabetic mouse model [4]. Hyperglycemia is known to induce diabetic complications, including hearing impairment. However, we hypothesize that insulin resistance, associated with hyperinsulinemia, induces different pathological impairments in the auditory system in the two types of DM. Furthermore, the electrophysiological differences between

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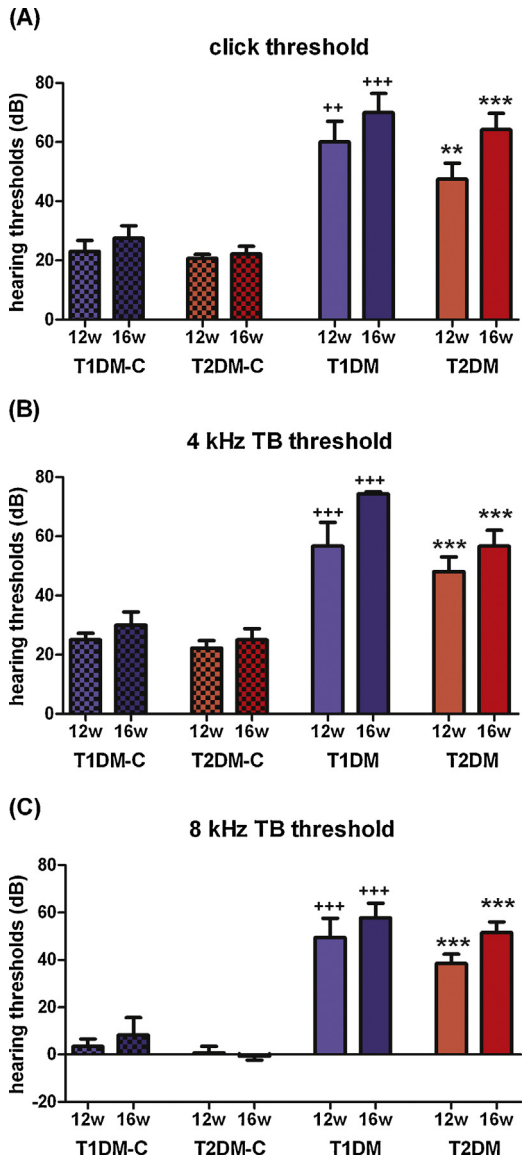

Fig. 1. *ABR hearing thresholds in response to clicks, 4 kHz TBs, and 8 kHz TBs in diabetic mice.* ABR hearing thresholds in response to stimulation with either clicks (A) 4 kHz TBs (B) or 8 kHz TBs (C) were measured. Data are expressed as means ± SEM. $^{++}$ $p < 0.01$ and $^{+++}$ $p < 0.001$ indicate significant differences from the T1DM-C group. ** $p < 0.01$ and *** $p < 0.001$ indicate significant differences from the T2DM-C group.

type 1 DM and type 2 DM were not addressed. In this study, we aimed to compare the auditory electrophysiological responses present in animal models of type 1 and type 2 DM. To quantify the extent of dysfunction and assess the specific auditory pathways impaired in each DM type, we performed electrophysiological auditory functional studies. Neurological evaluation of the ABR serves to assess the integrity of the peripheral auditory nerve and the lower part of the brain. Furthermore, assessment of the AMLR provides useful insight into the neurological function of the higher central auditory nervous system. Finally, we performed the TEOAE testing to directly measure cochlear function.

Materials and methods

All of the experimental procedures described here were performed in accordance with the Principles of Laboratory Animal Care (NIH publication, no. 80-23, revised 1996) and the Animal Care and Use Guidelines of Nambu University, Republic of Korea. Experimental mice were divided into four groups ($n = 10$/group). Seven-week old adult male ICR mice were divided as follows: STZ-induced diabetic mice as type 1 diabetic mice (T1DM), non-diabetic ICR mice as controls (T1DM-C), eight-week old adult male *Lepr* (+/+)*C57BL/KsJ* mice as type 2 diabetic mice (T2DM), male *Lepr*(±)*C57BL/KsJ* littermates as controls (T2DM-C) (Jung-Ang Lab Animal, Seoul, Republic of Korea). ICR mice were examined using an ABR test before STZ injection to confirm a normal hearing. A normal hearing mice ABR threshold level was considered to be ≤30 dB at clicks. A normal hearing ICR mice were induced with a single intraperitoneal injection of STZ at 150 mg/kg (Sigma Co., USA) dissolved in 0.01 M sodium citrate buffer (pH = 4.5) using a method described by Hong and Kang [4]. Mice were housed individually under a 12 h/12 h light/dark cycle, with *ad libitum* access to food and water. Blood glucose measurements from non-fasting mice were made from mouse tail pricks with strip-operated blood glucose sensors (ONETOUCH Ultra, Inverness Medical Ltd., UK). T1DM with blood glucose levels ≥300 mg/dl at one week after STZ injection were used in this study. Serum insulin levels were determined with insulin ELISA kits (Mercodia, Uppsala, Sweden).

Body weights and blood glucose levels were evaluated at 8 and 16 weeks old; insulin levels were determined at 16 weeks old in the T1DM, T1DM-C, T2DM, and T2DM-C groups. At 12 and 16 weeks old, peripheral and central auditory functions of all mice were tested. Auditory function tests were performed on anesthetized mice after *i.m.* administration of xylazine (0.43 mg/kg) and ketamine (4.57 mg/kg). Rectal temperatures were maintained at 37 ± 0.5 °C by using a heating lamp during testing.

Peripheral auditory functions and midbrain auditory functions were assessed through measurements of ABRs and AMLRs using a method described by Hong and Kang [4]. ABR parameters were

Table 1
Body weights, glucose levels, and insulin levels in diabetic mice.

Groups	Body weight (g)		Glucose levels (mg/dl)		Insulin level (μg/l)
	8 weeks	16 weeks	8 weeks	16 weeks	16 weeks
T1DM-C	28.44 ± 1.52	30.75 ± 1.35	136.86 ± 6.82	133.83 ± 6.21	2.94 ± 0.34
T1DM	29.50 ± 1.80	26.71 ± 1.22	564.14 ± 35.86^{+++}	≥600.00^{+++}	0.06 ± 0.01^{+++}
T2DM-C	20.50 ± 0.53	23.29 ± 0.47	201.29 ± 6.10	242.14 ± 19.03	3.69 ± 1.04
T2DM	43.25 ± 1.76$^{***,\#\#\#}$	50.00 ± 2.48$^{***,\#\#\#}$	352.86 ± 62.67*	424.63 ± 57.93**	16.79 ± 1.35$^{***,\#\#\#}$

Body weights, blood glucose levels, and insulin levels were measured in the following groups: STZ-induced type 1 diabetic mice (T1DM), non-diabetic ICR mice (T1DM-C), db/db type 2 diabetic mice (T2DM), and dbh mice (T2DM-C). Data are shown as means ± SEM.
$^{+++}$ $p < 0.001$ indicates a significant difference from the T1DM-C group.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$ indicate significant differences from the T2DM-C group.
$^{\#\#\#}$ $p < 0.001$ indicate significant differences from the T1DM group.