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Human ultrasonic hearing is induced by a direct ultrasonic stimulation of the cochlea

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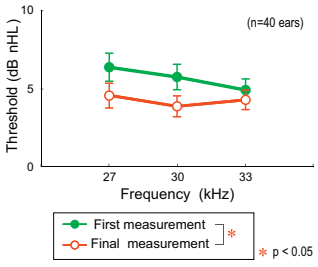
HIGHLIGHTS

- Thresholds for air-conducted sounds increased following the cisplatin administration.
- Thresholds for BCUs decreased following the cisplatin administration.
- The observed decrease in BCU threshold may be explained by the hypersensitivity.
- BCU thresholds were independent of a lower frequency sound due to non-linear process.
- Direct ultrasonic stimulation to the cochlea induces human ultrasonic perception.

GRAPHICAL ABSTRACT



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ABSTRACT

Ultrasound can be perceived by bone-conduction. The cochlear basal turn is involved in processing bone-conducted ultrasound (BCU) information. Previous studies have suggested that ultrasonic perception is induced by ultrasound itself. In contrast, it has also been suggested that a lower frequency sound is generated in non-linear process during the transmission pathway to the cochlea to induce an auditory sensations. To address this issue, we assessed cisplatin-induced changes in BCU sensitivity at 27, 30 and 33 kHz in 20 participants (40 ears) who were scheduled to undergo cisplatin chemoradiation therapy. Following the treatment, 62.5% ears were diagnosed with hearing loss according to the criteria of the American Speech-Language-Hearing Association. As expected, significant increases in sensitivity threshold were observed for air-conducted sounds ranging from 8 to 14 kHz. In contrast, the BCU threshold significantly decreased after the treatment. Considering that both air-conducted high-frequency sound and BCU are perceived in the cochlear basal turn, these findings indicate that ultrasonic perception is independent of hearing a lower frequency sound generated in non-linear process. In addition, our findings support the hypothesis that ultrasound itself induces ultrasonic perception in the cochlea. The observed cisplatin-induced increase in BCU sensitivity may be explained by hypersensitivity associated with outer hair cells' disorder.

Abbreviations: ANOVA, analysis of variance; ASHA, American Speech-Language-Hearing Association; BCU, bone-conducted ultrasound; IHC, inner hair cell; OHC, outer hair cell; USP, ultrasonic perception.

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1. Introduction

The maximum audible frequency detected by air-conduction in the human ear is approximately 24 kHz [29]. Sound above this frequency is termed "ultrasound". Ultrasound below 100 kHz is audible by bone conduction [5,7,9,24]. Several studies have described the characteristics of ultrasonic perception (USP). For example, the pitch of bone-conducted ultrasound (BCU) is independent of frequency and resembles that of air-conducted sound ranging from 8 to 16 kHz [6,7,10,24]. Interestingly, some individuals who are profoundly deaf can perceive BCU [2,12–14]. Furthermore, both normal individuals and the profoundly deaf can interpret BCU signals that are modulated by speech signals [14,23,31,32]. These findings indicate that there is potential for the development of a BCU hearing aid for profoundly deaf individuals. Although many studies have focused on this topic, the mechanisms of BCU perception have not been fully elucidated.

The peripheral organ that facilitates the perception of BCU has yet to be determined. That the pitch of BCU is similar to that of high-frequency audible sound is indicative of a role for the cochlear basal turn in BCU perception [7,24]. Investigations of air-conducted audition often employ a masking technique to identify the cochlear region responsible for hearing [16,17]. A similar approach may be useful to determine the cochlear region responsible for USP. If BCU excites the cochlear basal turn, then BCU would mask high-frequency air-conducted sound, and high-frequency air-conducted sound would conversely mask BCU. Our previous studies showed that ultrasound at 27, 30 and 33 kHz strongly masked air-conducted sounds ranging from 9 to 18 kHz [19], and that air-conducted sounds ranging from 8 to 16 kHz presented at an intensity of greater than 70 dB SPL masked 30 kHz BCU [20]. These results demonstrate that the cochlear region excited by BCU corresponds to the region excited by high-frequency air-conducted sounds.

The next issue of concern is whether USP is induced by ultrasound. Several studies have suggested the possibility that ultrasound is perceived by a lower frequency sound generated in non-linear process [7,10]. However, this theory does not explain why some profoundly deaf individuals who cannot hear air-conducted sound are able to hear BCU [13,18]. The masking of air-conducted sound produced by BCU indicated that the cochlea is excited by ultrasound itself, and not by a lower frequency sound [19]. This hypothesis has been strongly supported by animal research. For instance, Ohyama et al. [22] used electrocochleography to measure kanamycin-induced changes in the BCU hearing sensitivity for guinea pigs. If BCU perception is reliant on a lower frequency sound due to the non-linear process, the threshold of BCU will increase with the threshold of air-conducted sound. Ohyama et al. [22] found no significant changes in BCU hearing sensitivity, although kanamycin administration increased the threshold of air-conducted sound by approximately 30–60 dB. These findings indicate that USP is not induced by a lower-frequency sound due to non-linear process. However, the ultrasonic range of guinea pigs exceeds 50 kHz [11], which is very different from humans. A similar study, conducted with human participants, would be useful in clarifying the mechanisms of human USP.

From an ethical standpoint, the experimental administration of ototoxic drugs to individuals with normal hearing is impossible. However, similar drugs are sometimes used in medical treatments. By comparing hearing sensitivity between pre- and post-drug administration, the effect of these drugs on USP can be evaluated. Ototoxic drugs include aminoglycoside antibiotics, cancer chemotherapeutic agents, loop diuretics, and nonsteroidal anti-inflammatory drugs [30]. Among these, chemotherapeutic agents are frequently administered at carefully controlled doses. A common chemotherapeutic agent, cisplatin, is known to induce hearing loss [3,25–27,30]. Therefore, we chose to evaluate the effect of cisplatin on USP in patients who were scheduled to undergo chemoradiation therapy. The aim of this study was to determine whether USP is induced by ultrasound or by a low-frequency sound due to non-linear process. To our knowledge, this is the first investigation of the effect of ototoxic drugs on human USP. If USP is induced by a low-frequency sound due to non-linear process, then changes in BCU sensitivity would correspond to changes in sensitivity to air-conducted sound.

2. Materials and methods

2.1. Participants

Participants consisted of 20 hospitalized patients (40 ears in total) with a mean age of 63.0 years (ranging in age from 42 to 73 years) and 7 healthy individuals with normal hearing (14 ears in total) with a mean age of 30.8 years (ranging in age from 28 to 34 years). The patients suffered from head and neck cancer and received chemoradiation therapy with cisplatin at our hospital. The patients did not have any prior history of treatment with chemotherapeutic agents.

Table 1 shows the diagnosis, sex, age, cisplatin dose and total radiation dose of each patient. Cases 1–15 were treated with concurrent chemotherapy and radiotherapy. Chemotherapy consisted of 4–7 cisplatin cycles, with each cycle comprising 40 mg/m^2/day of cisplatin administered intravenously once a week. Radiotherapy consisted of 2.0 Gy per dose administered 5 times per week with a total of 58.0–70.0 Gy. In cases 1 and 4, the single cisplatin dose was decreased because of renal dysfunction. In cases 16–20, chemotherapy and radiation therapy were administered on alternating schedules. Chemotherapy consisted of 2–3 cycles, with each cycle comprising 50 mg/m^2/day of cisplatin over 2 days and 800 mg/m^2/day of 5-fluorouracil over 5 days, administered intravenously on consecutive days. Radiation therapy consisted of 1.8 Gy/day administered 5 times per week after the first chemotherapy cycle (adding up to 36.0 Gy), and 2.0 Gy/day 5 times per week after the second chemotherapy cycle (adding up to 34.0 Gy). The total exposure was 70.0 Gy. No other ototoxic drugs were administered to the patients.

This study was conducted with the approval of the Ethics Committee of Nara Medical University Hospital. All participants were provided with an explanation of the study and consent was obtained before conducting measurements.

2.2. Procedure

Hearing sensitivity was measured for air-conducted sound and BCU. The first measurement was obtained 1–7 days before the first cisplatin administration. During chemoradiotherapy, the follow-up measurements were carried out 5–6 days after each cisplatin administration. If the patient's physical condition was poor, the follow-up measurement was skipped. The final measurement was obtained 7–10 days after the final cisplatin treatment. The total number of measurements ranged from 3 to 8 (average 4.7). Hearing sensitivity was compared between the first and final measurements.

For the control group, measurements of hearing sensitivity for BCU were obtained once a week a total of 5 times.

2.2.1. Measurement of hearing sensitivity

For air-conducted sound, sensitivity measurements were obtained for sounds in the high-frequency range as well as for sounds in the conventional audiometric range. For sounds in the