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Establishment of a Gentamicin Cochlear Poisoning Model in Guinea Pigs and Cochlear Nerve Endings Recognition of Ultrasound Signals

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Data Interpretation D
Manuscript Preparation E
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Background: Aminoglycosides, a type of gram-negative antibacterial, are broad-spectrum antibiotics that are highly potent and have satisfactory therapeutic efficacy in the treatment of life-threatening infections. Our study aimed to establish a gentamicin-induced cochlear injury model and to investigate the cochlear nerve endings' recognition of ultrasound signals.

Material/Methods: A guinea pig cochlear injury model was established by intraperitoneal injection of gentamycin. Auditory brainstem response (ABR) and fMRI an affected cerebral cortex region of interest (ROI) of the cerebral cortex blood oxygenation level dependent (BOLD) effect was induced by bone-conducted ultrasound. Immunofluorescence was used to detect expression of Prestin in outer hair cells, Otoferlin in inner hair cells, and cochlear hair cell microfilament protein (F-Actin).

Results: For 30–35 KHz bone-conducted ultrasound, the induction rate of ABR threshold or ROI in the control group and the cochlear injury group was 40% and 0%, respectively, and for 80–90 KHz the induction rate was 20% and 20%, respectively. Gentamicin poisoning induced downregulation of expression of Prestin in cochlear outer cochlea, and Otoferlin and F-Actin in cochlear hair cells in different regions.

Conclusions: Gentamicin poisoning can cause different degrees of damage to cochlea hair cells in different regions. Guinea pigs with gentamicin poisoning can recognize high-frequency ultrasonic signals.

MeSH Keywords: Gentamicins • Guinea Pigs • Hair Cells, Ampulla • Sound

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Background

Clinical application of aminoglycosides causes hearing loss in nearly 120 000 people every year, and prevention and rehabilitation of cochlear damages caused by aminoguanidine drugs is particularly important and challenging in clinical practice [1]. Aminoglycosides not only damage auditory receptor cells, but also damage supporting cells, stria vascularis, and other types of tissue and cells [2]. Aminoglycosides also cause different degrees of injuries to different parts of the Corti organ [2]. The mechanism of aminoglycosides-induced hearing loss has been unclear, leading to poor outcomes of the prevention and treatment of those injuries. Postlingual deafness is common in patients with aminoglycosides-induced hearing impairment, even after timely treatment [3]. At present, application of electronic cochlea implants is very limited, and it is particularly important to seek appropriate rehabilitation measures for aminoglycosides-induced hearing loss. Compared with electronic cochlea implants, ultrasound hearing aids are noninvasive and lower-cost. However, the mechanism of endoscopic perception of ultrasound auditory is still controversial, and the hypothesis of the peripheral sensation of the relevant auditory system has not been confirmed.

At present, the application of ultrasound-assisted hearing aids is in the clinical trial stage, but rates of ultrasonic language recognition of patients with severe deafness are still low, which is closely related to peripheral perception of ultrasound signals and the unclear mechanism of central sensing [4]. Ohyma et al. reported the use of bone-conducted ultrasound signals (98.8 kHz and 143.5 kHz) to excite guinea pig ultrasound electrocochleogram, and concluded that the ultrasound peripheral receptor was located in the cochlea and the signal was recognized by cochlea hair cells [5]. Lenhardt et al. reported that a 40% sound recognition rate was achieved in severe sensorineural deafness patients with normal balloon function after the application of bone-conducted ultrasound hearing aids, indicating that the ultrasound peripheral sensor may be located in the balloon [6]. Nishimura et al. reported that bone-conducted ultrasound signals can be masked by high-frequency airway vocal sounds, suggesting that peripheral receptors of ultrasound are located in the cochlea [7]. However, there are also other studies showing that ultrasound signals can directly stimulate the spiral ganglion or brain stem cochlear nucleus, indicating that the peripheral ultrasound sensation is located in the spiral ganglion or brain stem nucleus [8]. Besides the ultrasound detection used in clinical practice, some numerical simulations are now used very widely. For instance, 3-dimensional simulation methods were used to detect multiple myeloma [9]. The *in silico* method can be considered in ultrasound detection as well, which may provide more insights in the future.

Aminoglycosides, a type of gram-negative antibacterial, are broad-spectrum antibiotics, are highly potent, and have satisfactory therapeutic efficacy in the treatment of life-threatening infections [10]. However, the use of aminoglycoside may cause adverse effects [11], among which inner ear toxicity affects 7% to 90% of users, depending of the specific type of antibiotic used [12]. Aminoglycosides damage the entire cochlea, with different degrees of injuries in different regions. However, the mechanism of aminoglycoside-induced cochlear injury is still unclear [13]. Most patients with severe hearing impairment caused by aminoglycosides will develop postlingual deafness, and application of electronic cochlear implants is greatly limited. Therefore, it is of great clinical importance to develop rehabilitation measures for aminoglycosides-induced hearing impairment.

The application of ultrasound hearing aids in hearing rehabilitation has attracted growing attention. However, the mechanism of endoscopic auditory perception of ultrasound is still controversial. At present, ultrasonic hearing aids have a low rate of sound recognition and are still far from clinical application. It has been hypothesized that the ultrasound peripheral receptor is located in the cochlea, and the signal is recognized by cochlear hair cells. However, other studies have shown that ultrasound signals can directly stimulate the spiral ganglion or brainstem cochlear nucleus, indicating that the peripheral ultrasound sensory area is located in the spiral ganglion or brainstem nucleus [14].

At present, only the cochlea has been proved to be a peripheral receptor of ultrasound signals, while the involvement of the vestibule is unknown. In addition, the mechanism underlying recognition of ultrasound frequency by the cochlea, especially by inner and outer hair cells, is unclear, and evidence at molecular levels is lacking. The frequency range recognized by guinea pigs is much wider than that of humans, which makes them an ideal model for ultrasound auditory studies [15]. In this study, a guinea pig cochlear injury model was established by intraperitoneal injection of gentamicin, and ABR threshold and ROI of BOLD effect were induced by ultrasound with different frequencies. Our study aimed to define the mechanism of gentamicin-induced cochlear hair cell injuries in guinea pigs, to explore the recognition of ultrasound signals by hair cells, and to provide a theoretical basis for the application of ultrasonic hearing aids in the rehabilitation of patients with deafness induced by amino nitrogen drugs.

Material and Methods

Experimental animals and grouping

Thirty healthy white guinea pigs of mixed sexes were used in this study. Those guinea pigs were 3 months old and weighed 250–300 g. All animals showed sensitive auricular reflex. Animals were randomly divided into a normal control group (n=10) and

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a gentamicin cochlear poisoning group (n=20). Animals in the gentamicin cochlear poisoning group were further divided into a 30–35 KHz bone-conducted ultrasound examination group (n=10) and an 80–90 KHz bone-conducted ultrasound examination group (n=10). Ultrasonic vibration was generated by a triggered function generator system (Leader LFG-1300s) and delivered to the animals through an ultrasonic transducer. The waveform of the signal was a sinusoidally enveloped random phase pip of 32.5 kHz and 85.0 kHz in 0.5 ms duration. The intensity of the ultrasonic stimulus was taken to be the peak-to-peak voltage of the signal at the amplifier output to the transducer, using a maximum peak-to-peak voltage of 20 V as the reference (0 dB).

Treatment

Animals in the gentamicin cochlear poisoning group were treated with intraperitoneal injection of 100 mg/kg gentamycin for 7 consecutive days to establish the cochlear gentamicin poisoning model. Auricle reflex and 24-h urine volume were recorded daily [14]. Animals in the control group were treated with the same amount of saline.

Induction of ABR threshold

ABR threshold measurement was performed using a TDT (System3) auditory evoked potential workstation with Pentusa Base Station as acquisition module and RX6 Multifunction Processor as the sound module. Frequencies exceeds 32 KHz were accessed to ultrasonic transmitters through external synchronization. The amplifier was A16PA and the attenuation module was PA5. Guinea pigs were anesthetized with 1% pentobarbital by intraperitoneal injection. Hair around the ears was removed and animals were fixed on a thermostat (temperature 38.5°C). Guinea pigs were moved into a quiet acoustic-electric-shielded room, and the collecting electrodes were placed on top of the skull. The ipsilateral auricular mastoid was measured as a reference electrode and the nasal root was a ground electrode. Acquisition magnification was 1000 k, the number of superposition was 500, and the test started from 20 db. Induction was performed using clicks, 30–35 kHz pulse square wave (pulse frequency was 100 times/s) and 80–90 kHz pulse square wave (pulse frequency was 100 times/s). Clicks were introduced from the left air-conducted earphone, and a 30–35 kHz pulsed square wave and 80–90 kHz pulsed square wave were introduced through bone conduction in the left mastoidal region, and ABR threshold determination was determined by v wave.

ROI detection of cerebral cortex BOLD induced by bone-conducted ultrasound in guinea pigs

Guinea pigs were anesthetized by isoflurane inhalation. Respiratory rate was maintained at 40–60 beats per min and the oxygen saturation was maintained above 90%. Magnetic resonance scanning was performed using the Bruker 7.0T systemic superconductor magnetic resonance imaging system. After a positioning scan, 30–35 kHz and 80–90 kHz bone-conducted pulsed square waves were used to induce cerebral cortex ROI. Induced parameters were TR2000 and TE20, with 600 repetitions, 20 min scanning time, acoustic stimulation for 20 s, and no acoustic stimulation for 10 s.

Immunofluorescence detection of Prestin, Otoferlin, and F-Actin proteins in cochlea hair cells

Guinea pigs were sacrificed immediately after ABR threshold and ROI detection. Auditory capsules were collected and fixed in 4% paraformaldehyde. After fixation for 8 h, the basement membranes of the left cochlea were collected for immunofluorescence detection of Prestin and Otoferlin proteins using primary antibodies, including rabbit anti-Prestin (1: 200, Santa Cruz, SC-30163) and mouse anti-Otoferlin (1: 200, Abcam, AB53233), and Alexa Fluor 568 conjugated goat anti-rabbit IgG secondary antibody (1: 1000, Molecular probe, A-11011). F-Actin fibroin fluorescence staining for the basement membranes of the right cochlea was performed using Alexa Fluor 488 Phallodini (1: 200, Molecular probe, A12379). Results were observed under a confocal microscope (Zeiss, LSM800).

Statistical analysis

Data are expressed as mean ±SEM. Comparisons among groups were performed using Sigma state software. We used the *t* test for comparisons among groups and $p<0.05$ indicated that a difference was statistically significant.

Results

Ultrasound-induced ABR threshold in normal control group and cochlear poisoning groups

ABR threshold induced by 30–35 kHz and 80–90 kHz pulse square waves in the normal control group was 35.71±4.17 and 66.43±4.67, respectively (Figure 1A), and induction rate was 40% and 20%, respectively. Significant differences were found in ABR threshold induced by ultrasound with different frequencies ($p<0.05$). In cochlear poisoning groups, the ABR threshold induced by 80–90 kHz pulse square waves was 71.27±5.38 with an induction rate of 20% (Figure 1B). The ABR threshold was not induced by 30–35 kHz pulse square waves.

ROI detection of bone-conducted ultrasound-induced cerebral cortex BOLD effect

In the normal control group, 30–35 kHz pulse square waves induced ROI of cerebral cortex BOLD effect in 3 animals (Figure 2A),

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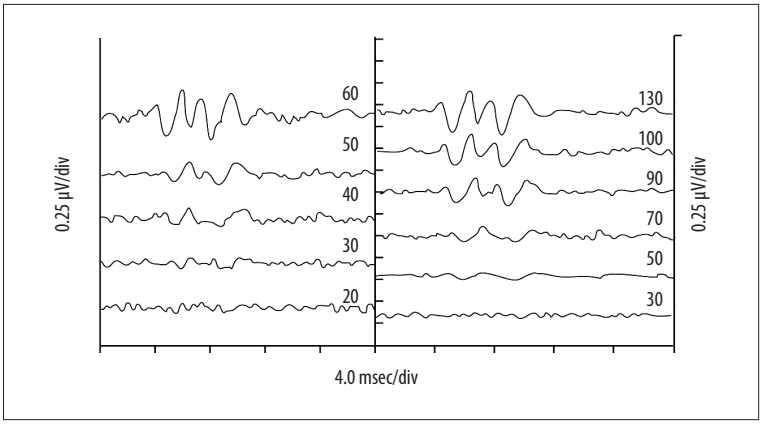

Figure 1. Representative auditory brainstem response (ABR) waveforms from 2 subjects. The left panel shows ABR waveforms of 30–35 kHz pulse square wave from subjects in the control group. The right panel shows ABR waveforms of 80–90 kHz pulse square waves from subjects in cochlear poisoning model groups. Numbers on the right side if the waveforms are stimulus level in dB nHL, and the thresholds were determined to be 30 and 70 db nHL, respectively, for the 2 groups.

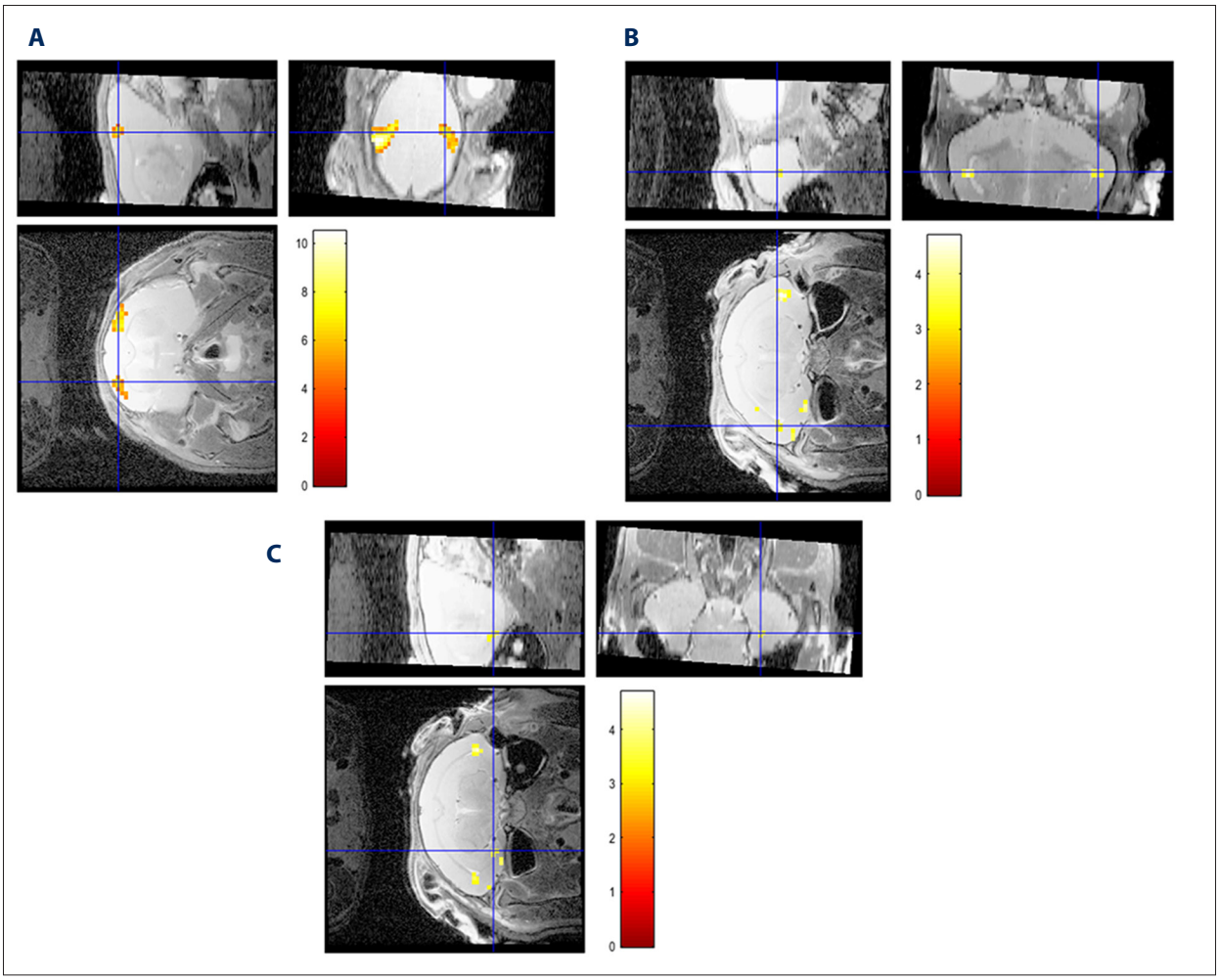

Figure 2. (**A**) ROI of cerebral cortex BOLD effect induced by 30–35 kHz pulse square in normal control group (109 voxels); (**B**) ROI of cerebral cortex BOLD effect induced by 80–90 kHz pulse square in cochlear poisoning group (6 voxels); (**C**) ROI of cerebral cortex BOLD effect induced by 80–90 kHz pulse square in cochlear poisoning group (16 voxels).

and 80–90 kHz pulse square waves induced ROI of cerebral cortex BOLD effect in 2 animals. In cochlear poisoning groups, 80–90 kHz pulse square waves induced ROI of cerebral cortex BOLD effect in 2 animals (Figure 2B, 2C), while ROI of cerebral cortex BOLD effect was not induced by 30–35 kHz pulse square waves.

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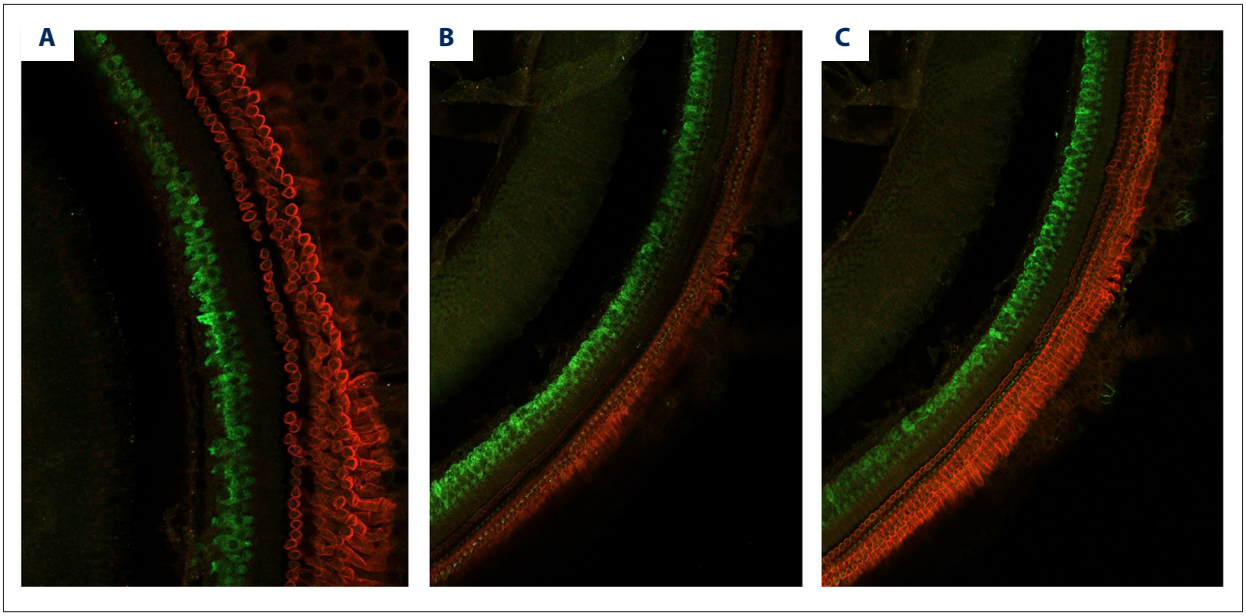

Figure 3. Immunofluorescence of Prestin (red) and Otofelin (green) in the 40±5 μm segment of cochlear hair cells. (**A**) Control, 950±10 μm to the initial segment of cochlear basilar membrane (400×); (**B**) Model, 95±10 μm to the initial segment of cochlear basilar membrane (200×); (**C**) Control, 95 μm ± 10 μm to the initial segment of cochlear basilar membrane (200×).

Immunofluorescence detection of Prestin, Otoferlin, and F-Actin proteins in cochlea hair cells of cochlear poisoning model

Fluorescent of Prestin (red) in cochlear outer hair cells and Otoferlin (green) in cochlear inner hair cells from the bottom of the basement membrane were 950±10 μm to 990 μms ±5 μm in the normal control group (Figure 3A). Fluorescent of Prestin (red) and Otoferlin (green) in cochlear hair cells from the bottom of the basement membrane was 95±10 μm to 135±5 μm, and was significantly attenuated in the cochlear poisoning group compared to the normal control group. The downregulation of the 2 proteins was more obvious in the areas closer to the initial segment of the cochlear basilar membrane in cochlear poisoning models than in controls (Figure 3B, 3C). In addition, from the beginning of the basement membrane, 800±10 μm to 840±5 μm F-Actin fluorescent staining of hair cells in the cochlear poisoning group was significantly attenuated compared with the normal control group. Phalloidin staining showed that the expression of F-Actin was also downregulated, and the downregulation was stronger in the areas closer to the initial segment of the cochlear basilar membrane in cochlear poisoning models than in controls (Figure 4A, 4B).

Discussion

In the research on ultrasonic hearing, studies related to ultrasonic perception and perceptual mechanisms have yielded conflicting results. Furthermore, the coding mechanisms of ultrasonic frequency and intensity by the cochlea have not yet been clarified. In our previous studies, we used bone-conducted ultrasound with different frequencies to treat normal guinea pigs, and found that different frequencies of bone-conducted ultrasound can decrease succinate dehydrogenase activity in hair cells and the decrease Prestin and Otoferlin protein expression in hair cells at different sites [16]. Thus, we successfully created a cochlear injury model related to ultrasonic frequency. The ABR and CAP thresholds of the experimental guinea pigs were evoked using clicks at 30 kHz and 80 kHz ultrasound. The 30 kHz-evoked ABR threshold was significantly higher in the 30 kHz ultrasonic cochlear injury group compared to the normal control group and the 80 kHz ultrasonic cochlear injury group. The difference in the 80 kHz-evoked ABR thresholds were not significant between the 30 kHz and 80 kHz ultrasonic cochlear injury groups. These results indicate that low-frequency ultrasound is perceived by cochlear hair cells, and the coding of frequency is determined by the spatial position of hair cells, whereas high-frequency ultrasound may not require the participation of cochlear hair cells [17].

We also used 50 kHz and 83 kHz bone conduction ultrasound to induce injury in normal guinea pigs, and examined the cerebral BOLD effect within a specific ROI. There were 4 (50 kHz) and 2 (83 kHz) bone conduction ultrasounds in 10 normal guinea pigs that were found to induce the cerebral cortex ROI, while 10 cases of the 50 kHz bone conduction ultrasound in the injury model failed to induce the cerebral cortex ROI. Only 2 cases of 83 kHz bone conduction ultrasound in the injury model induced the cerebral cortex ROI. The different frequencies of

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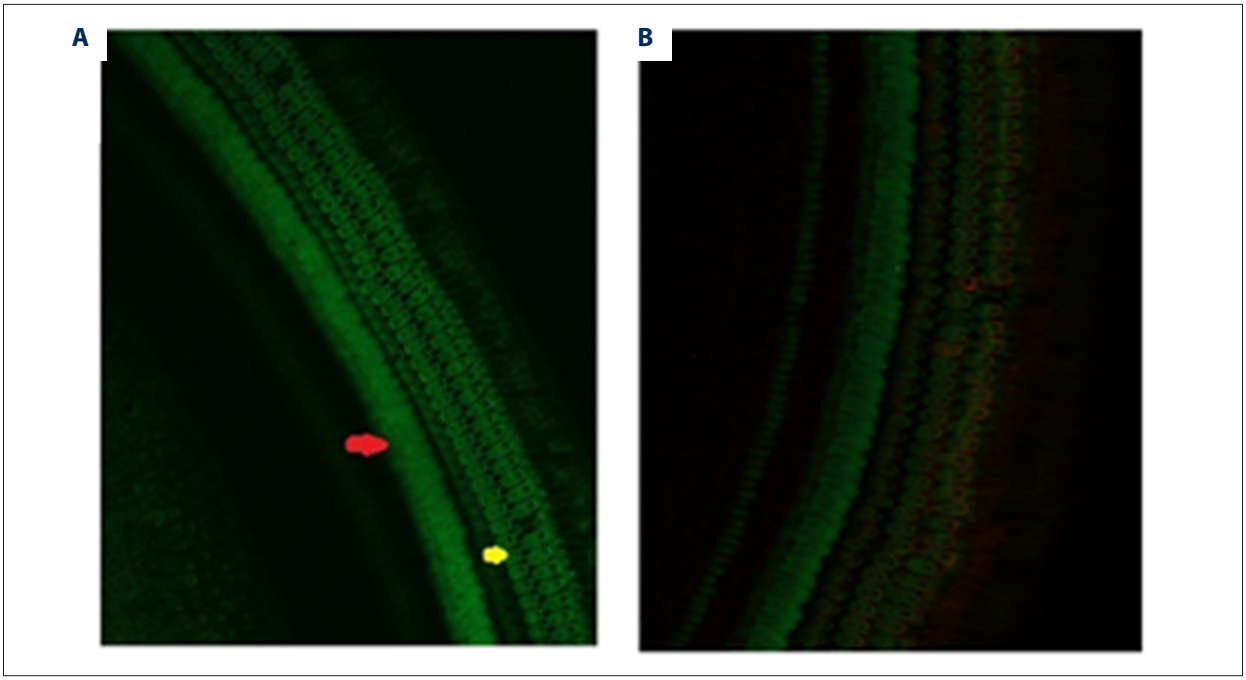

Figure 4. Phalloidin staining of F-Actin (green) in the 40±5 μm segment of cochlear hair cells (200×). (**A**) Control, 800±10 μm to the initial segment of cochlear basilar membrane; (**B**) Cochlea poisoning models, 800±10 μm to the initial segment of cochlear basilar membrane (200×). Red and yellow arrows indicate inner and outer hair cells, respectively.

bone conduction ultrasound signal-induced cerebral cortex ROI did not completely overlap, which indicates that the sensation of lower-frequency ultrasound requires the participation of peripheral cochlear hair cells, while higher frequencies require additional receptors [18].

In the present study, gentamicin was found to affect the whole cochlea and cause different degrees of damage to different regions of the cochlea. Because the spiral ganglion injury caused by gentamicin is secondary, it occurs later than that of hair cells. It appears that the hair cell damage is more serious than the spiral ganglion damage [19]. Gentamicin poisoning decreased expression of Prestin in the outer cochlea, as well as expression of Otoferlin and F-Actin in cochlear hair cells in different regions, and the decrease was more obvious in cochleae and less obvious in cupula cochleae. Our data are consistent with findings reported in previous studies. In the present study, BOLD ROI and ABR threshold of guinea pig cortex were induced by pulsed square waves with a frequency of 30–35 kHz and 80–90 kHz. We found that some normal guinea pigs can recognize both low-frequency and high-frequency ultrasound signals, but gentamicin-poisoning guinea pigs only perceive high-frequency ultrasound signals, indicating the involvement of cochlear hair cells in the recognition of lower-frequency ultrasound. Gentamicin may cause less damage to the spiral ganglion, and guinea pigs can recognize high-frequency ultrasound in spiral ganglion or higher-level central nerve nucleus.

Conclusions

Gentamicin poisoning decreased levels of Prestin, Otoferlin, and F-Actin in cochlear hair cells in different regions, and the decrease was more obvious in the cochleae and less obvious in the cupula cochleae. Gentamicin-poisoning guinea pigs can perceive high-frequency but not low-frequency ultrasound signals, indicating the involvement of cochlear hair cells in the recognition of lower-frequency ultrasound. Gentamicin may cause less damage to the spiral ganglion, and guinea pigs can recognize high-frequency ultrasound in the spiral ganglion or higher-level central nerve nucleus. Using numerical simulations in the detection could provide more insights in the near future. In our future work, we will use the *in silico* method.

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