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Experimental otoacoustic emission and auditory brainstem response changes by stellate ganglion blockage in rat

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Abstract

Introduction: To investigate the effect of stellate ganglion (SG) block on hearing in rats.

Materials and methods: Sixteen male adult rats were randomly divided into 2 equal groups. Both groups underwent preblock auditory brainstem responses (ABRs) in response to tone bursts at 4, 6, and 8 kHz and otoacoustic emissions in response to distortion products as a function of f2 frequency at 1, 2, 4, and 6 kHz. Local anesthetic (0.2 mL of 2% prilokain) was administered to the left SG of the study group by posterior cervical percutaneous approach for cervical sympathetic blockage. In the control group, 0.2 mL of physiological saline was injected to the left SG. Postblock hearing evaluations were made after 15 minutes of injections.

Results: Both Dp-gram and I/O function records suggested that whereas hearing thresholds were not affected in lower frequencies after SG blockage, it tended to increase at higher frequencies. In ABR records, waves I and II showed marked latency shift across all frequencies. The interpeak latency of waves I and II was shortened after blockage. Saline injection did not show any significant ABR or distortion-product otoacoustic emission threshold shift across frequencies at 60, 70, 80, and 90 dB sound pressure level.

Conclusion: Our data demonstrate that SG block improved the hearing parameters in rats with normal cochlear blood flow. To recommend SG blockage as a treatment option in the vascular pathologies of cochlea, further investigation should assess the efficiency of ganglion blockage in hearing parameters of rats with impaired cochlear blood flow.

1. Introduction

By stellate ganglion (SG) block (SGB), sympathetic supply of the head and neck, cervicothoracic region, and upper extremity is blocked reversibly, resulting in vasodilatation in those regions. This causes increased blood flow involving inner ear vessels [1]. The importance of cochlear blood flow increase as a treatment option in cochlear diseases such as sudden sensorineural hearing loss (HL), acoustic trauma, tinnitus, Meniere disease, noise-induced HL, and presbyacusis has been addressed in previous works [1-4]. Studies performed with Doppler flowmetry have shown that the cochlear blood flow was regulated by SG [5-8].

The SG in humans consists of the inferior cervical ganglion and the superior thoracic ganglion of the sympathetic nerve trunk. Because the rat does not posses ganglia corresponding to human SG and because middle and inferior cervical sympathetic ganglia produce effects similar to those of the SGB in humans, these ganglia are selected as targets for the blocks and named SG in rats [9].

In this study, we investigated the effect of SGB on cochlear blood flow and how hearing levels could be influenced by block in healthy rats. Impaired cochlear blood flow is assumed to be one of the principal causes of sensorineural HL. In the relevant literature, experimental studies have shown that distortion-product otoacoustic emissions (DPOAEs) and auditory brainstem responses (ABRs) are

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very sensitive index of cochlear ischemia [10-12]. In particular, Mom et al [11] showed that otoacoustic emission (OAE) more accurately reflected ischemic-induced alterations, the initial changes in the cochlear function than cochlear potentials. In this manner, we decided to investigate the effect of SGB on hearing parameters with DPOAE and ABR in rats with normal cochlear blood flow.

2. Materials and methods

2.1. Subjects and preparation

Twenty experimental rats (male Wistar rats approximately 3 months of age weighing 200–250 g) were acquired from a laboratory for experimental studies and housed in the same center after obtaining the approval for the study design from the animal ethics committee of our institution. Their room was maintained on a 12:12-hour light-dark cycle at 21°C and 30% to 60% humidity. The rats were sedated using ketamine (80 mg/kg Ketalar; Pfizer Ltd, Vienna, Austria) and xylazine (5 mg/kg Rompun; Bayer Ltd, Leverkusen, Germany) through intraperitoneal injection. Rats were immobilized in supine position on a rat bed with a soft, rough surface. Before testing, an otoscopic examination and transient OAE testing were performed on each animal. Only rats with normal outer ear canal and tympanic membrane in otoscopy and normal replicable transient OAE were included; therefore, the study was conducted with 16 rats.

2.2. Study design and SGB

Sixteen animals were randomly divided into 2 groups: control and study group; each consisted of 8 rats. In all rats, baseline DPOAE and tone-burst ABR measurements were performed before injection of SG. Blockage was performed with percutaneous Citanest (0.2 mL of 2% prilokain; Astra Zeneca, Stockholm, Sweden) injection in the study group. In the control group, physiological saline (0.2 mL) was injected in the same manner. Stellate ganglion was localized posteriorly, and block was performed via posterior percutaneous approach using the cartilaginous process of C7 spinous process as a landmark [13]. Left-side SG was chosen for blockage in all rats. Block was confirmed by development of ptosis and enophthalmos (as in Horner syndrome) at the same side in 1 to 2 minutes after blockage [9]. The OAEs and ABRs were recorded 5 and 10 minutes after the block from left ear of each rat.

2.3. OAE measurements

All measurements were recorded in a quiet room. The DPOAEs were elicited using a standard commercial ILO-96 OAE apparatus cochlear emission analyzer (Otodynamics Ltd, London, UK). Primary tones were introduced into the animal's outer ear canal through an insert earphone. The DPOAEs were generated by simultaneously presenting 2 sinusoids differing in frequency (f1 and f2) into the sealed ear canal of the rat. The distortion product at the 2f1-f2 frequency was measured. The intensities of primary stimuli were set as equilevel at 65 dB (L1 = L2). The frequencies were adjusted in such a manner that f2/f1 = 1.21. The DPOAEs were recorded as Dp-grams and I/O functions. Dp-gram ranged from 1001 to 6299. I/O functions were obtained by decreasing the primary tones from 66 to 36 dB sound pressure level (SPL) in 3-dB steps. The level of the noise floor was measured at a frequency 50 Hz more than the DPOAE frequency. Both types of testing methods were recorded until the response attained its highest level and were then terminated; no increase was noted [14]. For each rat, I/O functions at frequencies of 1, 2, 4, and 6 kHz were recorded.

2.4. ABR measurements

Auditory brainstem responses were obtained for both preblockage and postblockage conditions with a Nicolett Compact Four Electrodiagnostic system (Nicolett Biomedical Instrument, Madison, WI). Absolute latency of waves I and II and interpeak latency (IPL) of waves I to II were measured by an experienced otolaryngologist who was blinded to animal groups and stage of the experiment. Auditory brainstem responses were recorded in response to 3-millisecond (1/2/1 milliseconds rise/plateau/fall time) tone bursts at 4, 6, and 8 kHz. Tone-burst stimuli with intensities of 90, 80, 70, and 60 dB were delivered monaurally to the left ear through a closed acoustic system consisting of Nicolet tubal insert earphone with acoustic tubing and foam eartip. Stimuli were repeated 5 times per second, and a total of 512 trials were averaged during 20-millisecond analysis time using a custom signal averaging program. Band-pass filter was set at 100 to 2000 Hz. Responses were recorded between subdermal electrodes (platinum needle electrodes) at the vertex as positive electrode and the mastoid as reference electrode. The ground electrode was placed on the lower extremity muscle. Care was taken to attain electrode impedance and difference of interelectrode impedance less than 5 and 1 kΩ.

2.5. Statistical analysis

Postblockade data were compared with preblockade data to determine DPOAE amplitude changes and wave latency changes in each animal with Wilcoxon matched pair's signed rank test using SPSS program for Windows (Release 10.0, 1999, SPSS Inc). The shift in DPOAEs and ABRs of both groups was compared with one another using Mann-Whitney U test. All tests were performed 2 tailed. $P < .05$ was considered as significant.

3. Results

After the acquirement of recordings, the animals were closely observed until recovery from anesthesia. All animals tolerated the anesthesia and SGB well without any complication.

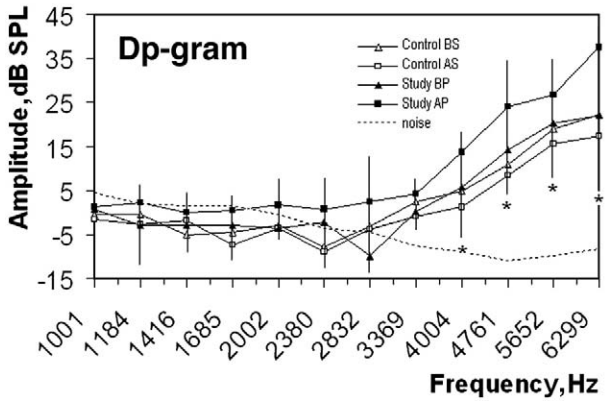

Fig. 1. Dp-grams measured from both the study and the control groups before and after SG injection.

3.1. DPOAE measurements

3.1.1. Dp-gram

Fig. 1 illustrates the effects of prilokain and saline injection on SG on Dp-gram. In saline-injected rats, there was no statistically significant change in DPOAE measurement after injection. However, prilokain injection caused significant DPOAE measurement alterations on higher frequencies (at 4004, 4761, 5652, and 6299 Hz; $P = .05$, $P = .05$, $P = .03$, and $P = .02$, respectively).

3.1.2. I/O functions

Fig. 2 illustrates the effects of prilokain and saline injection on SG on I/O functions at 1, 2, 4, and 6 kHz. At 1 kHz, there was no significant change on growth curves for both groups ($P > .05$) before and after SGB. At 2, 4, and 6 kHz, there was no significant change on growth rates in the control group. However, we observed some threshold increases in the study group after blockage. Study group animals showed marked hearing threshold shifts between 57 and 45 dB SPL primary stimulus levels ($P = .02$, $P = .01$, $P = .01$, $P = .03$, and $P = .05$, respectively) at 2-kHz frequency, at all primary stimulus levels at 4-kHz frequency excluding 36 dB SPL ($P = .20$), and at all primary stimulus levels at 6-kHz frequency excluding 48 dB SPL ($P = .06$).

3.2. ABR measurements

Figs. 3 and 4 and Table 1 demonstrate the effects of prilokain or saline injection on ABR measurements. In the study group, the absolute latency of wave I was significantly decreased at all tone-burst frequencies (4, 6, and 8 kHz) and all stimuli levels (60, 70, 80, and 90 dB) ($P < .03$). The latency shift of wave II was significant for all

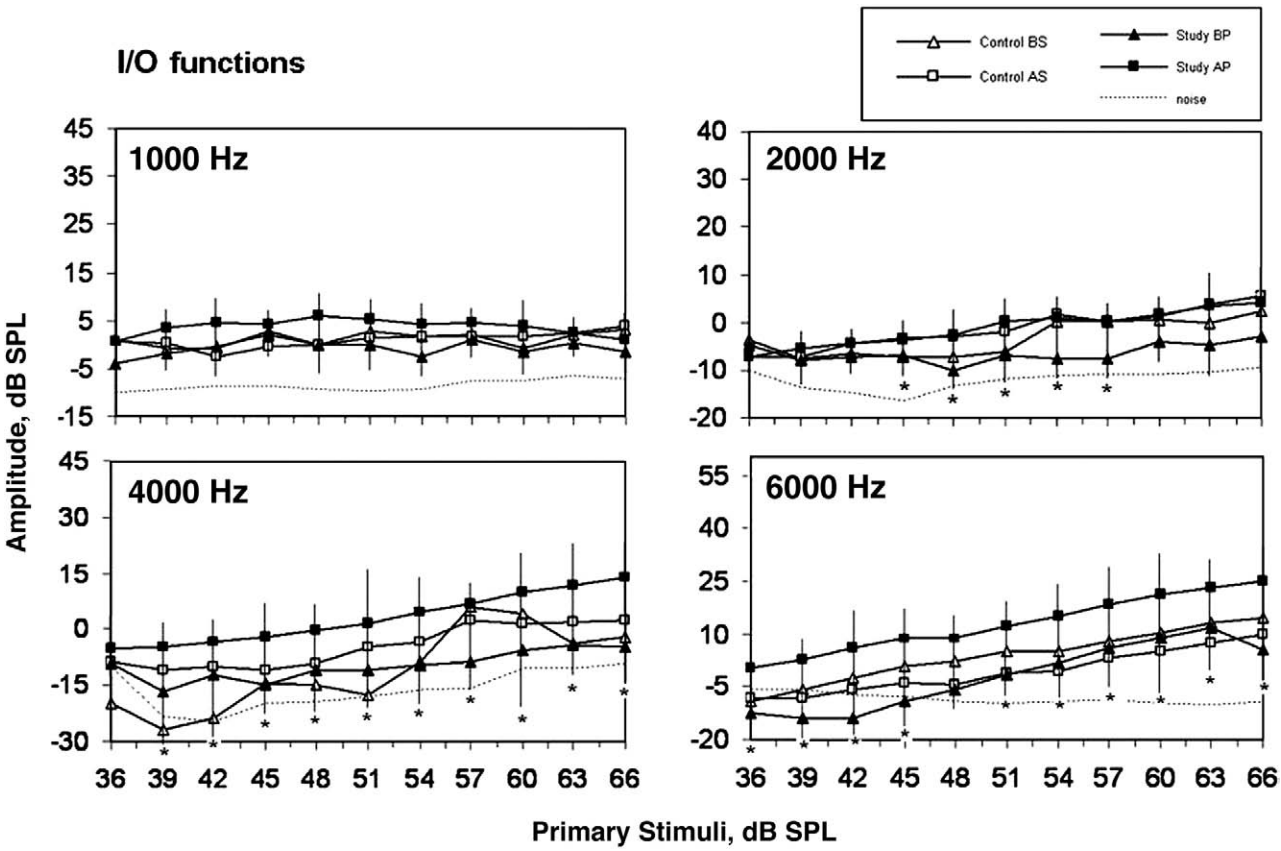

Fig. 2. I/O functions of the DPOAEs at 1-, 2-, 4-, and 6-kHz frequencies of both the study and the control groups before and after SG injection.

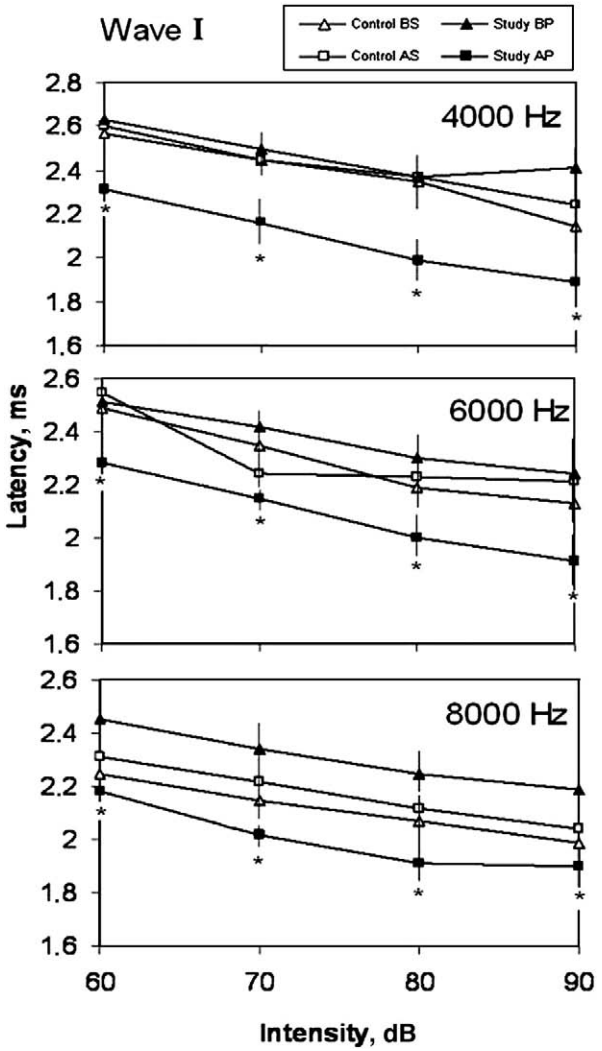

Fig. 3. Absolute latencies of wave I on tone-burst ABR at 4-, 6-, and 8-kHz frequencies of both the study and the control groups before and after SG injection.

SPLs at 4, 6, and 8 kHz ($P < .04$). In the control group, there was no significant effect of saline injection through SG across all frequencies and intensities on waves I and II latency ($P > .12$).

All IPLs of waves I and II were shortened after ganglion blockage in the study group. Statistical analysis of IPLs revealed significant change between preblock and postblock values only the at 90-dB tone-burst stimuli level in the study group ($P = .02$). In the control group, there was no statistically significant difference in any stimulus level ($P > .09$).

Both Dp-gram and I/O function records suggested that whereas hearing thresholds were not affected in lower frequencies, they tended to increase at higher frequencies because of SGB. In ABR records, waves I and II showed marked latency shift after SGB across all frequencies. The IPL of waves I and II was shortened after blockage in all stimuli levels. Stellate ganglion injection with saline did not show any significant ABR or DPOAE threshold shift.

4. Discussion

In the relevant literature, improvement in cochlear circulation after SGB has been reported. But its effect on hearing has not yet been shown by electrophysiological tests. In this study, we tried to figure out the effect of SGB on hearing parameters. We observed increased DPOAE thresholds and shortened ABR wave latencies and IPLs. Robust effects were observed on DPOAE and ABR threshold in SGB rats, and these effects seemed to be more pronounced on high frequencies. In Fig. 1, all Dp-gram plots for each

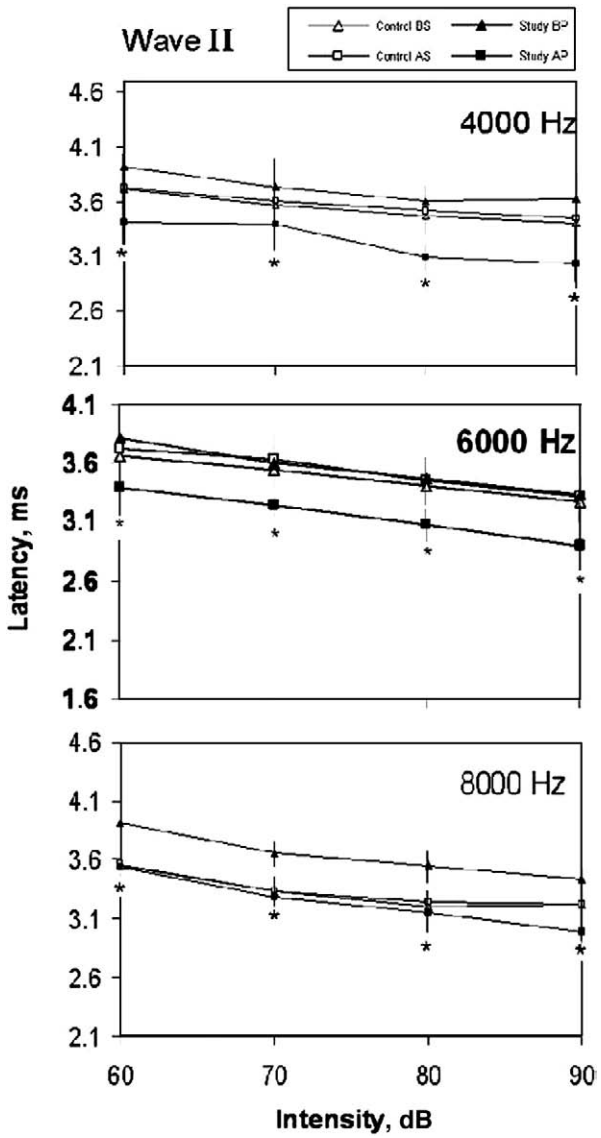

Fig. 4. Absolute latencies of wave II on tone-burst ABR at 4-, 6-, and 8-kHz frequencies of both the study and the control groups before and after SG injection.

Table 1
IPLs of wave I to II on tone-burst ABR at 4-, 6-, and 8-kHz frequencies of both the study and the control groups before and after SG injection

Wave I-II IPL	60 dB	70 dB	80 dB	90 dB
At 4000 Hz				
Control BS	1.18	1.21	1.21	1.26
Control AS	1.11	1.14	1.24	1.22
Study BP	1.19	1.23	1.23	1.22
Study AP	1.1	1.06	1.06	1.03 *
At 6000 Hz				
Control BS	1.2	1.2	1.23	1.2
Control AS	1.19	1.25	1.23	1.12
Study BP	1.23	1.18	1.14	1.08
Study AP	1.11	1.08	1.06	0.88 *
At 8000 Hz				
Control BS	1.3	1.31	1.25	1.22
Control AS	1.24	1.23	1.24	1.17
Study BP	1.25	1.27	1.29	1.25
Study AP	1.16	1.14	1.09	1 *

Control BS indicates control group before saline injection; control AS, control group after saline injection; study BP, study group before prilokain injection; study AP, study group after prilokain injection.

* Significant difference post–ganglion blocking with prilokain compared with the preblocking.

group showed typically an increase in amplitude at higher frequencies. This was consistent with the hearing measurements of Martin et al [14] in normal rats. This finding showed that SGB provided a marked healing on the hearing parameters of adult rats.

In Dp-grams, responses were obtained at constant tones (L1 = L2 = 65 dB) at different frequencies. In I/O functions, responses were obtained by decreasing the primary tones from 66 to 36 dB SPL in 3-dB steps and suprathreshold measures were obtained. An emitted response was accepted if the DPOAE was equal to or greater than 3 dB above the magnitude of the noise level for the Dp-gram and I/O functions. An amplitude of response higher than 3 dB above noise level showed robust response to the sound. A higher amplitude of response shows more robust response of hearing [15]. In the study group, after prilokain injection, we obtained higher amplitudes in all I/O functions and Dp-grams. Therefore, these findings represented improvement in the hearing of rats. Similar to our findings, hearing deterioration was accepted if there was any decline in the amplitude of responses [14,15]. Martin et al [14] demonstrated an amplitude loss in Dp-grams and assumed that this was because of worsening of hearing by aging. We concluded that increased amplitude of DPOAE responses represented “the healing effect on hearing.” Also, shortening of the wave latencies in ABR was accepted as improvement in hearing.

In the relevant literature, there are studies evaluating the efficiency of SGB in the management of cochlear HL. Those reports described SGB as a treatment option for tinnitus, presbyacusis, Meniere disease, noise-induced HL, and idiopathic sensorineural HL [16-19]. Most of the authors dealing with this topic worked on SGB’s effect on sudden sensorineural HL [20-28]. All of them agreed that hearing deficits were mainly caused by vascular insufficiency of cochlea. Also, in daily practice, the treatment protocols preventing vascular deficiency and improving the blood flow of inner ear are recommended. The major regulation mechanism of cochlear blood flow is via neural control [29-31]. A great number of adrenergic nerve fibers are present around the anterior inferior cerebellar, common cochlear, and spiral modiolar artery. These perivascular fibers originate from the superior cervical and/or stellate ganglia [1,2,30]. The blockage of cervical sympathetic nerves is responsible for the dilatation of cochlear vessels by activating the parasympathetic cholinergic fibers. Hearing improvement seems to be a result of cochlear blood flow increase. Kleinfeldt et al [32,33] had reported the cochlear microphonic potentials after SGB in normal and noise-induced ear in 2 studies in the German literature. Currently, there is no published experimental study in the relevant literature using electrophysiological tests to assess the effect of SGB on hearing impairments, although this approach can be easily applied in a rat model.

For monitoring the effects of SGB on the hearing of rats, we decided to use DPOAE or ABR measurements. We detected DPOAE alterations in postblock rats. This was most likely representing the increase in vascular supply to outer hair cells. An increase in DPOAE thresholds at a specific frequency region of the Dp-gram represents the focal alterations in the relevant region of the cochlea. An increase in suprathreshold amplitudes in DPOAEs was conceded as an improvement in hearing [16].

The frequency-specific threshold increase could be recorded by DPOAEs as in tone-burst ABRs. In addition to DPOAE measurements, responses to tone-burst stimuli were recorded with ABRs in SGB rats. In SGB rats, hearing alterations could be detected in relative specific frequencies by ABR and DPOAE recordings. Although different waves, amplitudes, or latencies were preferred in the construction of ABRs for experimental studies in the literature [9,29,34], we labeled the first 4 positive peaks (P1, P2, P3, and P4) according to the nomenclature adopted by Herr et al [35]. Because P1 and, partly, P2 were responsible for cochlear potentials, the latency of waves I and II was recorded, and shortening of the wave latencies was conceded as improvement in hearing. As expected, the latency shift was prominent for waves I and II. The IPL of waves I and II was shortened after blockage in all stimuli levels, although it was significant only at the 90-dB stimuli level. These findings show that the improvement in hearing was caused by cochlear effects rather than retrocochlear conditions.

In the literature investigating the interaction between cochlear blood flow and hearing, they observed significant improvement on hearing in higher frequencies response to increased cochlear blood flow. The higher frequencies affected more than lower frequencies did after blood flow increase [14,36]. We could speculate that increases, especially in higher frequencies, in both ABR and DPOAE

measurements were caused by increased cochlear blood flow after SGB.

A threshold study could be performed, but we preferred to do suprathreshold evaluation of hearing parameters. In our experimental design, we decided to evaluate the hearing alterations of rats with normal hearing. It could be observed more accurately at suprathreshold levels. We have chosen peak latencies after stimulation with 80-dB peak equivalent SPL at each frequency for statistical analysis. Latency prolongation in ABR waveforms was evaluated at constant stimulus level. Because initial threshold levels were normal, suprathreshold measurement was preferred. In addition, there were other studies evaluating latency prolongation or amplitude alteration at any stimulus level for statistical analysis, even in rats with abnormal hearing. However, ABR threshold shifts across all frequencies could be also studied in experimental ABR studies [37-39].

This study has some limitations. First, we are well aware of the limited frequency scale of our OAE and ABR devices. Using instruments with high frequency capacity would probably improve the detection of hearing alterations in an animal study like this. Also, our study and control groups consisted of a limited number of subjects. In addition, we studied the effect of SGB on rats with normal middle ear function. Our findings may not exactly represent the effect of ganglion blockage on subjects with hearing impairment.

The results of this study have shown that DPOAEs and ABRs were sensitive methods for measuring the auditory effects of SGB. Our findings revealing the electrophysiological alterations in rats after SGB supported the role of ganglion blockage in the treatment of patients with cochlear hearing problem, especially in sudden sensorineural HL. Further experimental studies should assess the efficiency of ganglion blockage in rats with impaired hearing and the electrophysiological alterations after SGB in humans.

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