THE EFFECT OF TINNITUS AND PRESBYCUSIS ON CONTRALATERAL SUPPRESSION OF OTOACOUSTIC EMISSIONS

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Abstract

Background: The medial olivocochlear system (MOCS), part of the efferent auditory pathway, causes an inhibitory effect on the outer hair cells, thus protecting them against extreme noise exposure and improving speech discrimination in noisy environments. This study aims to assess the MOCS function and aging in tinnitus patients with the use of contralateral suppression (CS) of otoacoustic emissions (OAEs).

Material and methods: 136 subjects took part in this study, divided in 6 groups (control group, right-side tinnitus, left-side tinnitus, bilateral tinnitus, presbycusis without tinnitus and presbycusis with tinnitus). CS of transiently- evoked (TEOAEs) and distortion products OAEs (DPOAEs) was measured for each group and pair- wise comparisons between the groups were performed.

Results: CS was less frequent and the mean values of CS were significantly lower in the tinnitus ears than normal ones. The mean values of CS of ears with presbycusis were in some cases higher than ears with presbycusis and tinnitus and also than ears with tinnitus and normal hearing. Not particular statistical differences were found between the method used (TEOAEs or DPOAEs) and the comparisons between the groups.

Conclusions: The absence and lower values of CS in tinnitus ears imply a MOCS dysfunction as a main factor of tinnitus generation. Tinnitus seems to have a more detrimental effect to the MOCS function than presbycusis. CS of TEOAEs and DPOAEs are equally sensitive methods in detecting MOCS dysfunction in patients with tinnitus.

Key words: efferent pathways • otoacoustic emissions (spontaneous) • presbycusis, tinnitus

EL IMPACTO DEL TINNITUS Y DE LA PÉRDIDA AUDITIVA ASOCIADA A LA EDAD EN LA SUPRESIÓN CONTRALATERAL DE OTOEMISIONES ACÚSTICAS

Resúmen

Introducción: El sistema olivococlear medial (MOCS), un elemento de la vía auditiva eferente, tiene un efecto inhibidor sobre las células ciliadas auditivas externas, y, de esta manera, las protege contra los sonidos altos y mejora la comprensión del habla en el ruido. El objetivo del presente estudio es la evaluación del impacto de MOCS y del impacto de la edad en los pacientes con el tinnitus, mediante la supresión contralateral (CS) de las otoemisiones acústicas.

Materiales y métodos: En la prueba han participado 136 personas, divididas en 6 grupos: grupo de control, grupo con el tinnitus en el oído derecho, con el tinnitus en el oído izquierdo, con el tinnitus bilateral, con la pérdida auditiva asociada a la edad sin el tinnitus y con la pérdida auditiva asociada a la edad y con el tinnitus. En cada grupo se ha analizado la supresión contralateral de las otoemisiones acústicas evocadas transitorias (TEOAE) y de las otoemisiones acústicas de productos de distorsión (DPOAE). Se ha realizado, también, el estudio comparativo entre los grupos.

Resultados: El efecto CS era menos frecuente, y el valor medio de CS fue considerablemente más bajo en los pacientes con el tinnitus, en comparación con aquellos sin el tinnitus. En algunos casos, los valores medios de CS en los pacientes con la pérdida auditiva asociada a la edad fueron mayores que en aquellos con la pérdida auditiva asociada a la edad y con el tinnitus,

y superiores a los valores de aquellos con el tinnitus y con el oído correcto. No se han observado diferencias estadísticamente relevantes entre los métodos aplicados (TEOAE o DPOAE) y en las comparaciones entre los grupos.

Conclusiones: La relativa falta de CS y valores más bajos de CS en las personas con el tinnitus señalan al trastorno de MOCS como el factor principal en la generación del tinnitus. Resulta entonces, que el tinnitus tiene un impacto más perjudicial sobre el MOCS que la pérdida auditiva asociada a la edad. CS en el caso de TEOAE o DPOAE es también un método sensible para determinar las alteraciones de MOCS en los pacientes con el tinnitus.

Palabras clave: vía eferente • otoemisión acústica (espontánea) • pérdida auditiva asociada a la edad • tinnitus

ВОЗДЕЙСТВИЕ УШНЫХ ШУМОВ И ТУГОУХОСТИ, СВЯЗАННОЙ С ВОЗРАСТОМ НА КОНТРАЛАТЕРАЛЬНУЮ СУПРЕССИЮ ОТОАКУСТИЧЕСКОЙ ЭМИССИИ

Изложение

Введение: Медиальный оливоулитковый путь (MOCS), который является элементом слухового эфферентного пути, имеет тормозящее воздействие на внешние слуховые клетки, тем самым предохраняет их от высоких звуков и улучшает понимание речи в шуме. Целью настоящего исследования является оценка действия MOCS и влияния возраста у пациентов с ушными шумами с помощью контралатеральной супрессии (CS) отоакустической эмиссии.

Материал и методы: В исследовании взяло участие 136 человек, которые были разделены на 6 групп: контрольную, с ушными шумами в правом ухе, с ушными шумами в левом ухе, с двусторонними ушными шумами, с тугоухостью, связанной с возрастом без ушных шумов и с тугоухостью, связанной с возрастом и ушными шумами. В каждой группе исследовано CS отоакустических эмиссий, вызванных треском (TEOAE) и эмиссий продуктов нелинейной деформации (DPOAE). Проведены также сравнительные исследования между группами.

Результаты: У пациентов с ушными шумам эффект CS реже проявлялся, а среднее значение CS было значительно ниже в сравнении с пациентами без шумов. В нескольких случаях средние значения CS у пациентов с тугоухостью, связанной с возрастом были выше, чем у тех с тугоухостью, связанной с возрастом и ушными шумами, а также выше, чем у пациентов с шумами и нормальным слухом. Особенных, статистически существенных отличий между использованным методом (TEOAE и DPOAE), а также в сравнениях между группами не наблюдалось.

Итоги: Относительное отсутствие CS и меньшие значения CS у пациентов с ушными шумами показывают расстройство MOCS в качестве главного фактора в генерации ушных шумов. Следовательно, оказывается, что ушные шумы имеют более негативное воздействие на MOCS чем тугоухость, связанная с возрастом. CS, в случае TEOAE или DPOAE, является столь же чутким методом при определении расстройств MOCS у пациентов с ушными ушами.

Ключевые слова: эфферентный путь • отоакустическая (непосредственная) эмиссия, тугоухость • связанная с возрастом, ушные шумы

WPŁYW SZUMÓW USZNYCH I NIEDOSŁUCHU ZWIĄZANEGO Z WIEKIEM NA SUPRESJĘ KONTRALATERALNĄ EMISJI OTOAKUSTYCZNEJ

Streszczenie

Wprowadzenie: Przyśrodkowy układ oliwkowo-ślimakowy (MOCS), który stanowi element słuchowej drogi eferentnej, ma hamujący wpływ na zewnętrzne komórki słuchowe, a tym samym chroni je przed wysokimi dźwiękami i poprawia rozumienie mowy w szumie. Celem niniejszego badania jest ocena działania MOCS oraz wpływu wieku u pacjentów z szumami usznymi za pomocą supresji kontralateralnej (CS) emisji otoakustycznej.

Materiał i metody: W badaniu udział wzięło 136 osób, które zostały podzielone na 6 grup: kontrolną, z szumami usznymi w prawym uchu, z szumami usznymi w lewym uchu, z obustronnymi szumami usznymi, z niedosłuchem związanym z wiekiem bez szumów usznych, oraz z niedosłuchem związanym z wiekiem i szumami usznymi. W każdej grupie badano CS emisji otoakustycznych wywołanych trzaskiem (TEOAE) oraz emisji produktów zniekształceń nieliniowych (DPOAE). Wykonano również badania porównawcze pomiędzy grupami.

Wyniki: Efekt CS rzadziej występował, a wartość średnia CS była istotnie niższa u pacjentów z szumami usznymi w porównaniu do osób bez szumów. W kilku przypadkach średnie wartości CS u pacjentów z niedosłuchem związanym z wiekiem były wyższe niż u tych z niedosłuchem związanym z wiekiem i szumami usznymi oraz wyższe niż u pacjentów z szumami i słuchem normalnym. Nie zaobserwowano szczególnych statystycznie istotnych różnic pomiędzy wykorzystaną metodą (TEOAE lub DPOAE) i w porównaniach pomiędzy grupami.

Wnioski: Relatywny brak CS oraz niższe wartości CS u osób z szumami usznymi wskazują na zaburzenie MOCS jako głównego czynnika w generacji szumów usznych. Okazuje się zatem, że szumy uszne mają bardziej szkodliwy wpływ na MOCS niż niedosłuch związany z wiekiem. CS w przypadku TEOAE lub DPOAE jest równie czułą metodą przy określaniu zaburzeń MOCS u pacjentów z szumami usznymi.

Słowa kluczowe: droga eferentna • emisja otoakustyczna (spontaniczna) • niedosłuch związany z wiekiem • szumy uszne

Background

Tinnitus is one of the commonest and most ancient of symptoms, but its origins remain unknown. Many definitions have been given: the perception of a sound without an external stimulus [1], the conscious experience of a sound coming from the head [2], or a phantom noise produced in the auditory system due to aberrant neural activity or stimulation.

The cochlea has been considered the origin of subjective tinnitus. It is the organ which receives and produces sounds, and the factors leading to hearing loss may also lead to tinnitus. For example, noise exposure, head trauma, and ototoxicity may cause tinnitus. Recent theories suggest a lack of coordination between the outer and inner hair cells as a possible triggering factor. According to the discordant dysfunction theory, the outer hair cells are more vulnerable to damage than the inner hair cells, so an auditory lesion will affect mainly the former, causing an imbalance of function [3]. This theory is supported by multiple studies which show smaller otoacoustic emission amplitudes (TEOAEs and DPOAEs) in tinnitus patients compared to normal hearing people [4,5]. Other recent theories link spontaneous otoacoustic emissions (SOAEs) with the generation of tinnitus. This idea is based on the fact that individuals with higher recorded SOAEs are more likely to present tinnitus, so spontaneous activity indicates an increased possibility for developing tinnitus [6].

Furthermore, the perception of tinnitus is thought to be related to changes in the patterns of activity in the central auditory system, activity which is perceived as sound [7]. Plastic changes and reorganization of the tonotopic maps at the level of the auditory cortex are also implicated. Participation of the emotions, especially anxiety, stress, and depression, has been known for many years. The involvement of the limbic system and its role in the morbidity and clinical severity of tinnitus have been shown by studies of stress and psychiatric disorders [8]. Habituation is a defence mechanism that is absent in patients with clinically severe tinnitus [9], with the 5-hydroxytryptamine (5-HT) system playing an important role in the process [10]. Habituation differentiates the patient's tolerance and reaction towards tinnitus [11] and this mechanism is used in Tinnitus Retraining Therapy (TRT).

This study focuses on the theory of insufficiency of inhibitory auditory mechanisms in tinnitus patients. These inhibitory effects are mostly performed by the efferent auditory system, which consists of the lateral and the medial olivocochlear system, together forming the olivocochlear bundle. The medial olivocochlear system (MOCS) innervates the outer hair cells, thus modulating their micromechanical properties and the gain of the cochlear amplifier and having an inhibitory effect on their spontaneous activity. Other effects of the MOCS include protection against moderate noise and better sound and speech discrimination in noisy environments [12,13]. Other studies suggest that insufficient activity of the MOCS may be present in children with specific language impairment or reading disabilities [14,15].

Dysfunction of the MOCS is thought to be a triggering factor in generating tinnitus. Using surgery on animals, Maison et al. [16] found that reduced activity in the efferent auditory pathway made animals more vulnerable to acoustic injury and tinnitus. They also showed that these animals were protected against noise damage and tinnitus by a nicotinic-a-9-cholinergic receptor, which enhances efferent cochlea activity and which it is expressed in outer hair cells. MOCS activity is usually assessed by a reduction in otoacoustic emissions (OAEs) from simultaneous contralateral noise, a process known as contralateral suppression (CS) of otoacoustic emissions. A range of studies have shown a smaller OAE reduction in tinnitus patients than in normal people [17–20], thus implying an efferent dysfunction. When contralateral noise is applied to tinnitus patients, OAEs (either transiently evoked or distortion products) undergo a slight reduction, or even an increase (enhancement), in comparison with normal individuals, although there are also studies which detect no statistically significant differences [21,22]. The findings in the literature are therefore equivocal. In all the above mentioned studies, a variety of protocols have been used to evaluate the function of MOCS, which probably explains the diversity of results – it all depends on the type and intensity of the suppressor stimuli used.

Assessment of MOCS dysfunction can be performed with either transiently evoked OAEs (TEOAEs) or distortion product OAEs (DPOAEs). It can also be qualitative or quantitative (estimating either the presence or the values of suppression respectively). The patient groups examined can also vary, including categories such as unilateral or bilateral tinnitus, and the tinnitus can have different etiologies, or be associated with different audiological features. A recent review [23] assessed 15 relevant studies in terms of the groups examined and the evaluation methods used, and found a remarkable heterogeneity of protocols,

a feature which explains the divergent findings on the role of the MOCS in the generation of tinnitus.

The aim of this study was to assess the function of MOCS in patients with either bilateral or unilateral tinnitus and in patients with presbycusis and tinnitus, by comparing the CS of TEOAEs and DPOAEs with those of the control groups at multiple frequencies. The assessment was carried out by comparing both the presence and the amplitudes of the CS. Additional comparisons were performed concerning i) the differences of suppression values depending on the age, and ii) the sensitivity of TEOAEs and DPOAEs to detect statistically important differences of suppression in tinnitus patients.

Material and methods

Exactly 136 adults took place in this study, which was performed in the audiology department of the ENT clinic of Hippocration University Hospital in Athens from 2007–10. The patients provided voluntary consent after approval of the Scientific Committee of Ethics of the hospital. Only right-handed people were included in the study, in order to minimize the influence of the lateralization of the MOCS (which depends on which side of the brain is dominant). For the same reason, in the case of unilateral tinnitus the suffering ear was compared only with the same ear of the control group. The people who participated in the study were divided into six groups as follows:

Group C, which was the control group, consisted of 28 normal-hearing people without tinnitus (15 of which, or 54%, were women) with a mean age of 42 years and S.D.=13.

Group R which included 13 people with tinnitus at the right ear, consisting of 7 women and 6 men (58% women) with a mean age of 43 years and S.D=16.

Group L included 26 people with tinnitus at the left ear of which 16 were women (62%) and 10 were men. The mean age of the group was 48 years and S.D.=12.

Group B included 37 people with bilateral tinnitus, 21 women and 16 men (57% and 43% respectively) with a mean age of 46 years and S.D.=12.

Group P included 13 people with presbycusis without tinnitus, which was the control group for the group with tinnitus and presbycusis, with a mean age of 60 years and S.D.=6.

Group Q included 19 people with presbycusis who suffered from tinnitus, with a mean age of 63 years and S.D=7.

All subjects underwent audiometry and tympanometry with middle ear muscle reflex in order to exclude middle ear pathology and to estimate the threshold at which the reflex was activated.

The patients (groups R, L, B, and Q) had subjective tinnitus that had been experienced for more than 3 months and had no middle ear or retrocochlear pathology. The groups C, R, L, and B were people who presented normal audiograms (hearing thresholds below or equal to 20 dB), while groups P and Q were people with presbycusis, i.e. normal hearing thresholds at low frequencies and gradual sloping sensorineural hearing loss at high frequencies (thresholds for group P at 1 kHz: 24 dB with SD=4 dB; at 2 kHz: 33 dB with SD=5 dB; and at 4 kHz: 40 dB with SD=5 dB. For group Q at 1 kHz: 25 dB with SD=3 dB; at 2 kHz: 35 dB with SD=5 dB; and at 4 kHz: 42 dB with SD=6 dB).

All subjects included in the study underwent TEOAEs and DPOAEs, first without contralateral white noise and afterwards with the presence of contralateral white noise as stimuli for suppression of otoacoustic emissions. OAEs were measured in a sound-treated booth with an ILO v6 apparatus (Otodynamics Ltd). TEOAE responses were elicited by linear click stimuli of 60 dB SPL. TEOAE measurements were automatically terminated after 260 responses had been obtained. The frequency bands measured were centered at 1, 1.4, 2, 2.8, and 4 kHz. DPOAEs were elicited by two tones of 65 and 55 dB (L1 and L2, respectively) and the distortion products 2f1–f2 (f2/f1 ratio=1.22) were gathered at frequencies 1, 1.4, 2, 2.8, 4, 5, and 6 kHz. TEOAE and DPOAE measurements were considered valid only when there was a probe stability of 90% or better and the emission amplitude exceeded the noise floor by at least 6 dB (SNR ≥6 dB). Measurements of TEOAEs and DPOAEs were performed in the presence of contralateral white noise of 50 dB SL generated by an Amplaid A321 twin channel diagnostic audiometer (Amplifon, Milan, Italy). The intensity of this suppressor was below the threshold of the middle ear muscle reflex for all subjects. CS was estimated by subtracting the value of OAEs with contralateral white noise from the value of OAEs without contralateral noise. Zero or negative values implied lack of suppression.

All statistical calculations were performed using SPSS version 14.0 (SPSS Inc., Chicago, USA). Associations between a group and lack of suppression of otoacoustic emissions were tested by the use of contingency tables and the calculation of chi-square tests without the correction of continuity. All possible post hoc pair-wise comparisons between the 6 groups were conducted by the chi-square test to determine the groups in which there was a statistically significant difference in the percentage of patients who experienced lack of suppression of otoacoustic emissions. The association between the lack of suppression of otoacoustic emissions and the method used to measure otoacoustic emissions (i.e. TE or DP) was tested by using the McNemar test. Associations between otoacoustic emissions (treated as a continuous variable) and the group were evaluated through one-way analysis of variance (ANOVA) when continuous variables were normally distributed or Kruskal-Wallis when they were skewed. All possible post hoc pair-wise comparisons between the 6 groups were conducted through Student's *t*-test for normally distributed variables or Mann–Whitney for skewed variables, to determine the groups among which there was a statistically significant difference in mean values of otoacoustic emission suppression. In all post hoc pair-wise comparisons, the Bonferroni correction was used in order to account for increase in Type I error.

Repeated measures analysis of variance (RMANOVA) was conducted to examine the interaction between the method used to measure otoacoustic emissions and the group, namely whether the differences between groups were affected by the method used to measure otoacoustic emissions. A probability value of 5% was considered statistically significant.

Table 1. Lack of suppression of otoacoustic emissions in the right ear (percent of subjects, n/N)

Hz	Method	Group						*p*-values
		C	R	L	B	P	Q	
1 kHz	TE	25.9% (p=0.002)§	76.9% (p=0.002)*	32.0% (p=0.002)§	40.5% (15/25)	9.1% (p=0.001)§	13.3% (p=0.001)§	**0.003**
	DP	28.6% (8/28)	23.1% (3/13)	20.0% (5/25)	42.6% (15/35)	22.2% (2/9)	5.6% (1/18)	0.087
	p-value	0.999	0.016	0.453	0.999	0.999	0.999	
1.4 kHz	TE	22.2% (6/27)	46.2% (6/13)	36.0% (9/25)	37.8% (14/37)	23.1% (3/13)	29.4% (5/17)	0.605
	DP	10.7% (p=0.002)†	30.8% (4/13)	29.2% (7/24)	44.4% (p=0.002)*	10.0% (1/10)	6.3% (p=0.003)†	**0.011**
	p-value	0.508	0.687	0.774	0.754	0.625	0.125	
2 kHz	TE	21.4% (6/28)	61.5% (8/13)	26.9% (7/26)	40.5% (15/37)	0% (p=0.001)§,†	18.8% (3/16)	**0.009**
	DP	34.6% (9/26)	30.8% (4/13)	33.3% (8/24)	51.4% (19/37)	11.1% (1/9)	27.3% (3/11)	0.241
	p-value	0.508	0.219	0.687	0.388	0.999	0.999	
2.8 kHz	TE	21.4% (6/28)	30.8% (4/13)	37.5% (9/24)	30.6% (11/36)	8.3% (1/12)	16.7% (2/12)	0.425
	DP	15.4% (4/26)	53.8% (7/13)	25.0% (6/24)	47.2% (p=0.009)*	0% (p=0.008)§, (p=0.009)†	28.6% (2/7)	**0.011**
	p-value	0.687	0.453	0.453	0.332	–	0.999	
4 kHz	TE	26.9% (7/19)	16.7% (2/12)	50.0% (12/24)	44.4% (16/20)	20.0% (2/10)	25.0% (1/4)	0.194
	DP	25.9% (7/27)	54.5% (6/11)	35.0% (7/20)	55.9% (19/34)	22.2% (2/9)	25.0% (1/4)	0.129
	p-value	0.999	0.063	0.289	0.227	0.999	–	
5 kHz	DP	36.0% (9/25)	33.3% (1/3)	46.7% (7/15)	75.0% (15/20)	33.3% (2/6)	–	0.091
6 kHz	DP	54.2% (13/24)	66.7% (2/3)	64.3% (9/14)	81.0% (17/21)	40.0% (2/5)	–	0.298

n – number of participants with lack of suppression of otoacoustic emissions; *N* – total number of participants (excluding those who had no otoacoustic emissions); * compared to group C; § compared to group R; ‡ compared to group L; † compared to group B (all calculations after adjustment for multiple comparisons based on Bonferroni correction)

Results

Comparisons of the presence of suppression

The right ear of group R was found (at 1 kHz) to present a lack of CS more frequently than the right ear of groups C and L when TEOAEs were used (p=0.002). Moreover, when DPOAEs were used the right ear of group B presented a lack of suppression more frequently (at 1.4 and 2.8 kHz) than the right ear of group C (p=0.002 and 0.009 respectively) (Table 1).

The left ear of group L experienced a lack of suppression more frequently (at 1 and 1.4 kHz) than the left ear of group R when TEOAEs were used (p=0.04 and 0.006) and at 2.8 kHz with DPOAEs (p=0.004). At 4 kHz, the suppression was found to be less frequent for the left ear of group L in comparison with group C (p=0.001). At 2 kHz Group B lacked suppression at the left ear more frequently than group C with both TEOAEs and DPOAEs (p=0.002 for both) and at 2.8 kHz when DPOAEs were used (p=0.008). It also lacked suppression more often than the left ear of group R at 1 kHz when TEOAEs were used and at 2.8 kHz when DPOAEs were used (p=0.001 and 0.002 respectively) (Table 2).

Comparisons of the mean values of suppression

The mean values of CS at the right ear were lower in group R than in group C at 1.4, 2, 2.8, and 4 kHz when TEOAEs were used (p<0.001, p=0.004, 0.009, and 0.005 respectively) and at 1, 1.4, 2, and 4 kHz when DPOAEs were used (p<0.001 for the first two and p=0.002 for the last two respectively). The mean values of suppression of the right ear were significantly lower in group R than in group L at 1.4, 2.8, and 4 kHz (p=0.002, 0.002, and 0.007 respectively) when TEOAEs were used and at 1 and 1.4 kHz with DPOAEs (p<0.001). Moreover, the right ear of group B

Table 2. Lack of suppression of otoacoustic emissions in the left ear (percent of subjects, n/N)

Hz	Method	Group						p-values
		C	R	L	B	P	Q	
1 kHz	**TE**	22.2% (6/27)	0% (0/12)	48.0% (p=0.04)§	55.6% (20/36)*,§	22.2% (2/9)	18.8% (3/16)	**0.001**
	DP	22.2% (6/27)	12.5% (1/8)	33.3% (8/24)	34.3% (12/35)	12.5% (1/8)	6.7% (1/15)	0.247
	***p*-value**	0.999	–	0.388	0.143	0.999	0.500	
1.4 kHz	**TE**	14.3% (4/28)	0% (0/12)	44.0% (p=0.006)§	27.8% (10/36)	0% (0/12)‡	17.6% (3/17)	**0.007**
	DP	14.8% (4/27)	8.3% (1/12)	44.0% (11/25)	37.8% (14/37)	0% (0/11)‡	7.1% (1/14)	**0.004**
	***p*-value**	0.999	–	0.999	0.581	–	0.500	
2 kHz	**TE**	14.3% (4/28)	16.7% (2/12)	44.0% (11/25)	51.4% (p=0.002)*	0% (0/14)‡†	14.3% (2/14)	**0.001**
	DP	7.4% (2/27)	25.0% (3/12)	30.8% (8/26)	41.7% (p=0.002)*	11.1% (1/9)	18.2% (2/11)	**0.047**
	***p*-value**	0.625	0.999	0.581	0.424	–	0.999	
2.8 kHz	**TE**	14.3% (4/28)	7.7% (1/13)	26.9% (7/26)	25.0% (9/36)	8.3% (1/12)	7.7% (1/13)	0.358
	DP	18.5% (5/27)	0% (0/12)	47.8% (p=0.004)§	51.4% (p=0.008)*, (p=0.002)§	10.0% (1/10)	0% (0/6)	**0.001**
	***p*-value**	0.687	–	0.344	0.022	–	–	
4 kHz	**TE**	28.6% (8/28)	18.2% (2/11)	58.3% (14/24)	51.4% (18/35)	22.2% (2/9)	25.0% (1/4)	0.063
	DP	23.1% (6/26)	27.8% (3/11)	69.9% (p=0.001)*	55.6% (20/36)	12.5% (1/8)‡	100% (1/1)	**0.003**
	***p*-value**	0.999	0.999	0.727	0.999	0.999		
5 kHz	**DP**	45.0% (9/20)	16.7% (1/6)	64.7% (11/17)	70.6% (12/17)	60.0% (3/5)	–	0.150
6 kHz	**DP**	50.0% (9/18)	25.0% (1/4)	72.2% (13/18)	88.2% (15/17)§	50.0% (2/4)	–	0.050

Symbols as per Table 1

presented lower amounts of suppression in comparison with the right ear of group C at 1, 1.4, 2, and 2.8 kHz when TEOAEs were used (p=0.001, p<0.001, p= 0.006, p=0.003) and at 1, 1.4, 2, 2.8, and 4 kHz with DPOAEs (p=0.002, p<0.001, p=0.004, p=0.003, p=0.006) (Table 3).

The mean values of CS at the left ear were lower in group L than in group C at 2 kHz and 2.8 kHz with TEOAEs and at 1, 2, 2.8, and 4 kHz with DPOAEs. The left ear of group B also presented statistically significantly lower values of suppression than the left of group C and group R at all frequencies between 1 and 4 kHz with both TEOAEs and DPOAEs (Table 4).

When the mean values of suppression of both ears were compared, group B presented statistically significantly lower values than group C at all frequencies between 1 and 4 kHz with both TEOAEs and DPOAEs (Table 5).

Comparisons of groups P and Q

The mean values of suppression were found to be lower in group Q than in group P in the right ear at 1.4 kHz with DPOAEs (p=0.008), and at the left ear at 2 kHz with TEOAEs and at 1.4 and 2 kHz with DPOAEs (p=0.004, 0.005, and 0.006 respectively). When the mean values of both ears were compared, statistically significant differences were found only at 2 kHz with TEOAEs (Tables 3–5).

Comparisons of groups P and R, L, B

The percentage of lack of suppression was higher for the right ear of group R than the right ear of group P at 1 and 2 kHz with TEOAEs and at 2.8 kHz with DPOAEs. It was also higher for the left ear of group L than the left ear of group P at 1.4 kHz with TEOAEs and at 1.4 and 4 kHz with DPOAEs (Tables 1, 2).

Table 3. Amount of suppression of otoacoustic emissions in the right ear in dB (mean ± standard deviation)

Hz	Method	Group						p-values
		C	R	L	B	P	Q	
1 kHz	TE	3.6±2.2 (n=20)	2.1±0.1 (n=3)	4.1±2.5 (n=17)	1.8±1.2 (p=0.001)*‡	3.5±2.4 (n=10)	1.7±1.1 (n=13)*,‡	**0.001**
	DP	3.0±1.4 (n=20)	0.95±0.81 (p<0.001)*	2.4±0.9 (p<0.001)§	1.7±0.9 (p=0.002)*	2.0±1.0 (n=7)	1.1±0.8 (n=17)*,‡	**<0.001**
	***p*-value**	0.999	0.250	0.022	0.302	0.125	0.146	0.176
1.4 kHz	TE	4.1±1.9 (n=21)	1.2±0.7 (p<0.001)*	4.3±2.8 (p=0.002)§	1.7±1.0 (p<0.001)*‡	3.1±1.9 (n=10)§	1.9±1.0 (n=12)*	**<0.001**
	DP	3.4±1.9 (n=25)	0.9±0.4 (p<0.001)*	3.4±2.8 (p<0.001)§	1.8±1.0 (p<0.001)*	2.3±1.1 (p=0.005)§	1.3±0.6 (p=0.008)*,‡,#	**<0.001**
	***p*-value**	0.999	0.999	0.508	0.804	0.999	0.754	0.881
2 kHz	TE	4.1±2.7 (n=22)	1.3±0.7 (p=0.004)*	3.6±2.9 (p=0.002)	2.2±1.4 (p=0.006)*	3.8±3.1 (n=12)	1.5±1.0 (n=13)*	**0.002**
	DP	3.4±1.6 (n=17)	1.5±0.7 (p=0.002)*	3.5±2.3 (n=16)	1.8±0.9 (p=0.004)*	2.0±0.7 (n=8)	1.4±0.9 (n=8)*‡	**<0.001**
	***p*-value**	0.791	0.625	0.791	0.999	0.727	0.687	0.693
2.8 kHz	TE	3.2±2.2 (n=22)	1.4±0.6 (p=0.009)*	3.2±1.6 (n=15) §	1.6±1.2 (p=0.003)*,‡	3.6±2.7 (p=0.009)†	2.0±0.9 (n=10)	**0.001**
	DP	3.0±1.5 (n=22)	1.8±0.8 (n=6)	2.9±1.7 (n=18)	1.5±0.8 (p=0.003)*,‡	2.8±1.1 (p=0.009)†	1.2±0.8 (n=5)	**0.003**
	***p*-value**	0.332	0.125	0.774	0.774	0.999	0.125	0.703
4 kHz	TE	2.8±2.2 (n=19)	1.1±0.8 (p=0.005)*	2.8±1.9 (p=0.007)§	1.5±0.8 (n=20)	3.1±2.3 (p=0.009)§	1.2±0.3 (n=3)	**0.009**
	DP	3.4±2.6 (n=20)	0.9±0.6 (p=0.002)*	2.9±2.9 (n=13)	0.9±0.9 (p=0.006)*	2.4±0.9 (n=7)§,†	0.9±0.2 (n=3)	**<0.001**
	***p*-value**	0.999	0.999	0.219	0.227	0.999	–	0.288
5 kHz	DP	2.9±2.1 (n=16)	0.5±0.4 (n=2)	2.9±1.4 (n=8)	1.2±0.7 (n=5)	2.1±1.3 (n=4)	–	0.068
6 kHz	DP	3.3±1.8 (n=11)	1.1 (n=1)	2.0±1.2 (n=5)	1.1±0.7 (n=4)	1.8±0.9 (n=3)	–	0.115

Compared to group P (calculated after adjusting for multiple comparisons based on Bonferroni correction). Other symbols as per previous tables

The mean values of suppression were lower for the right ear of group R compared to the right ear of group P at 1.4 and 4 kHz with both TEOAEs and DPOAEs. They were also lower for group B compared to group P at 2.8 kHz with both TEOAEs and DPOAEs. Suppression was also lower in group B than in group P when the left ear was examined at 1.4 and 2 kHz with TEOAEs and at 2 kHz with DPOAEs. Finally, the mean value of suppression of both ears was lower in group B than in group P at 1.4, 2, and 2.8 kHz with TEOAEs and at 2, 2.8, and 4 kHz with DPOAEs.

Comparisons between DPOAEs and TEOAEs as methods of assessing olivocochlear function

Statistically significant differences between the two methods were only found at 1 kHz in group R when the percentage of lack of suppression was examined at the right ear (Table 1) and at 2.8 kHz in group B when this percentage was examined at the left ear (Table 2). A higher percentage was estimated by TEOAEs in the former and by DPOAEs in the latter. When the mean values of suppression were assessed, it was found that the method did not affect the comparisons between groups at the right ear, while at the left statistically significant differences were found at 1 and 2.8 kHz (p=0.039 and 0.045 respectively) (Table 4).

All the other differences in pair-wise comparisons, not mentioned, were found to be statistically not significant.

Discussion

The MOCS branch of the efferent auditory system, which arises mostly from the contralateral superior olivary complex, provides the outer hair cells with their main innervation. As mentioned, the MOCS acts as an inhibitor of the activity of outer hair cells and its stimulation reduces the amplitude of otoacoustic emissions. Suppression of OAEs with contralateral noise seems to be an objective and non-invasive method of MOCS function assessment, since Collet et al. [24] observed that OAE amplitude can be reduced by contralateral noise. This property disappears after resection of the olivocochlear bundle [25]. Nevertheless,

Table 4. Amount of suppression of otoacoustic emissions in the left ear in dB (mean ± standard deviation)

Hz	Method	Group						*p*-values
		C	R	L	B	P	Q	
1 kHz	TE	3.7±2.3 (n=21)	3.9±1.8 (n=12)	2.5±2.2 (n=13)	1.9±1.2 (p=0.004)*§	2.4±1.2 (n=7)	2.1±0.9 (n=13)§	**0.009**
	DP	3.9±2.2 (n=21)	1.9±0.6 (n=7)	1.7±0.8 (p=0.001)*	1.6±0.8 (p<0.001)*	3.3±1.6 (n=7)	1.4±0.9 (n=14)*	**<0.001**
	p-value	0.607	0.016	0.727	0.344	0.625	0.109	**0.039**
1.4 kHz	TE	4.0±2.4 (n=24)	3.1±1.2 (n=12)	2.4±1.5 (n=14)	1.6±1.1 (p<0.001)*,§	2.7±1.4 (p=0.007)†	2.2±1.1 (n=14)	**<0.001**
	DP	3.1±1.9 (n=23)	2.9±1.4 (n=11)	2.9±1.4 (n=14)	1.5±1.0 (p<0.001)*,§,‡	2.4±1.2 (n=11)	1.0±0.9 (p=0.005)*,§,‡,#	**<0.001**
	p-value	0.263	0.754	0.999	0.629	0.999	0.344	0.385
2 kHz	TE	4.4±2.7 (n=24)	3.9±1.7 (n=10)	1.6±0.8 (p=0.001)*,§	1.6±0.9 (p<0.001)*,§	3.2±2.1 (p=0.003)‡,†	1.4±1.0 (p=0.004)*,§,#	**<0.001**
	DP	3.8±2.1 (n=25)	3.1±1.7 (n=9)	1.9±1.1 (p=0.001)*	1.2±0.8 (p<0.001)*,§	2.8±1.2 (p=0.001)†	1.2±0.6 (p=0.006)*,§,#	**<0.001**
	p-value	0.832	0.727	0.999	0.388	0.727	0.289	0.919
2.8 kHz	TE	2.9±1.7 (n=24)	3.2±1.1 (n=12)	1.5±1.0 (p=0.001)*,§	1.5±0.8 (p<0.001)*,§	2.5±1.4 (n=11)	1.5±0.8 (n=12)*,§	**<0.001**
	DP	3.8±2.2 (n=22)	2.5±0.8 (n=12)	1.9±1.5 (p=0.009)*	1.5±0.8 (p<0.001)*,§	2.4±0.6 (n=9)	2.0±0.8 (n=6)	**0.001**
	p-value	0.263	0.227	0.999	0.607	0.999	0.999	**0.045**
4 kHz	TE	2.7±2.0 (n=20)	2.4±0.9 (n=9)	1.4±1.1 (n=10)	1.4±1.0 (p=0.007)*,§	2.1±0.6 (n=7)	1.5±1.5 (n=3)	**0.019**
	DP	3.4±2.5 (n=20)	2.7±1.0 (n=8)	1.9±1.3 (p<0.001)*	1.2±0.8 (p=0.002)*,§	1.9±0.7 (n=7)	–	**0.008**
	p-value	0.999	0.625	0.999	0.999	0.687		0.436
5 kHz	DP	3.4±2.4 (n=11)	2.7±1.7 (n=5)	1.9±2.2 (n=6)	0.9±0.6 (n=5)*	2.3±1.1 (n=2)	–	0.068
6 kHz	DP	4.0±2.1 (n=9)	2.2±1.0 (n=3)	1.6±0.9 (n=5)	3.1±0.8 (n=2)	1.3±0.4 (n=2)	–	0.076

Symbols as per previous tables

as presented in the study by Guinan et al. [26], there are three limitations in the use of contralateral suppression of OAEs for assessing MOCS: a) the use of contralateral suppression examines only a part of the MOCS; b) the elicitor stimuli for the OAE may also activate the medial olivocochlear reflex; and c) both the probe and the contralateral sound may elicit the middle ear muscle reflex. They conclude with some suggested methods to eliminate these confounding factors based on stimulus-frequency otoacoustic emissions.

Another property of the MOCS, which is important for planning any study and assessing its results, is its asymmetry. As shown by Khalfa [27], there is a right-side dominance in young, right-handed adults. This asymmetry, known as lateralization of MOCS, means that in normal right-handed individuals their right ears exhibit higher OAE suppression values than left ears [28]. Therefore, especially in the case of unilateral tinnitus, comparisons should always be made between the same ears of the tinnitus group and the control group, and never between the healthy ear and the suffering ear of the tinnitus group. Otherwise, the difference would either be underestimated in the case of right-side tinnitus, or overestimated in the case of left-side tinnitus.

In the present study qualitative (presence or absence of suppression) and quantitative (mean value of suppression) comparisons have been performed between all groups in order to answer the question of how MOCS is affected in tinnitus patients and which method (TEOAE or DPOAE) is more sensitive to detect these changes.

In the group with right unilateral tinnitus (R), we observed a lack of suppression at the right ear more frequently than in group C (the control group) or group L (left unilateral tinnitus) at 1 kHz; furthermore, in group L lack of suppression was more frequent at the left ear than in group C at 1.4 kHz with TEOAEs and at 4 kHz with DPOAEs. The left ear of group L lacked suppression more frequently compared to group R at 1 kHz and 1.4 kHz with TEOAEs and at 2.8 kHz with DPOAEs. These results show that in the case of unilateral tinnitus, the suffering ear does not present suppression with contralateral white noise as often

Table 5. Amount of suppression of otoacoustic emissions in both ears in dB (mean ± standard deviation)

Hz	Method	Group				
		C	B	P	Q	*p*-values
1 kHz	TE	3.9±1.4 (n=17)	1.9±0.9 (p=0.003)*	2.9±1.8 (n=7)	1.9±0.6 (p<0.001)*	**0.001**
	DP	3.6±1.3 (n=17)	1.7±0.7 (p<0.001)*	2.8±1.1 (n=5)	1.3±0.7 (p<0.001)*	**<0.001**
	p-value	0.999	0.999	0.500	0.125	0.361
1.4 kHz	TE	4.2±1.5 (n=18)	1.7±0.7 (p<0.001)*	3.0±1.2 (p=0.002)†	2.1±0.8 (p<0.001)*	**<0.001**
	DP	3.4±1.3 (n=20)	1.7±0.7 (p<0.001)*	2.3±1.2 (n=7)	1.0±0.5 (p<0.001)*	**<0.001**
	p-value	0.267	0.999	0.357	0.219	0.167
2 kHz	TE	3.9±2.0 (n=18)	1.6±0.7 (p<0.001)*	3.4±2.4 (p=0.001)†	1.6±0.7 (n=9)*,#	**<0.001**
	DP	3.4±1.3 (n=16)	1.2±0.5 (p<0.001)*	2.6±0.7 (p=0.002)†	1.6±0.7 (n=3)	**<0.001**
	p-value	0.999	0.625	0.999	0.999	0.936
2.8 kHz	TE	3.2±1.6 (n=20)	1.6±0.7 (p<0.001)*	3.2±1.8 (p=0.002)†	2.0±0.7 (n=7)	**<0.001**
	DP	3.4±1.3 (n=18)	1.7±0.5 (p<0.001)*	2.7±0.5 (p=0.004)†	1.9±0.3 (n=3)	**<0.001**
	p-value	0.424	0.999	0.453	0.999	0.316
4 kHz	TE	3.3±1.5 (n=13)	1.5±0.9 (p=0.002)*	2.9±1.6 (n=5)	0.95 (n=1)	**0.014**
	DP	3.5±1.9 (n=15)	1.2±0.6 (p=0.002)*	2.5±0.2 (p=0.003)†	–	**0.004**
	p-value	0.219	0.625	0.999		0.803
5 kHz	DP	3.1±2.3 (n=6)	0.35 (n=1)	1.4 (n=1)	–	0.130
6 kHz	DP	3.8±2.3 (n=3)	2.2 (n=1)	1.0 (n=1)	–	0.344

Symbols are per previous tables

as the control group of healthy normal-hearing adults, or even, at some frequencies, as the healthy same ear of the group with unilateral tinnitus at the opposite ear. The same observation can be made for the group with bilateral tinnitus (B), whose right ear lacked suppression more often compared to group C at 1.4 and 2.8 kHz with DPOAEs, and whose left ear lacks suppression more often compared to group C at 2 kHz with both TEOAEs and DPOAEs and at 2.8 kHz with DPOAEs. These results indicate that at some frequencies the ears of patients with bilateral tinnitus tend to present suppression less often than the control group, or even the healthy ears of people with unilateral tinnitus (e.g. the left ear of group B and R at 1 kHz with TEOAEs and at 2.8 kHz with DPOAEs).

Several studies [19,29,30] have used comparisons of percentage of suppression between groups as a method to assess the function of the MOCS. Favero et al. [29], using DPOAEs, found statistically significant differences of the percentage of suppression between tinnitus and non-tinnitus subjects at all frequencies except for 1 and 6 kHz. In our study, differences of this percentage were observed only at some frequencies, even though both TEOAEs and DPOAEs were used (1 kHz for group R, 1.4 kHz with TE and 4kHz for group L, and 1.4, 2, and 2.8 kHz for group B). The explanation may be, first, an inadequate number of participants and, second, the fact that either a lack of suppression or a reduction is expected at every frequency. Both these two possibilities cannot easily happen: at some frequencies OAEs of tinnitus patients are not suppressed (and perhaps enhanced) in the presence of contralateral white noise; at other frequencies they are suppressed, but not as much as the control groups, as we show below. Lalaki et al. [30] found abnormal suppression of TEOAEs in people with idiopathic tinnitus more frequently than in normal subjects, but much less frequently than in people with noise-induced tinnitus. Ceranic et al. [19] found a lower percentage of suppression in people with tinnitus after head injury compared to normal subjects or people with head injury but without tinnitus.

Similar results came from a study by Riga et al. [20] where DPOAEs contralateral suppression was not statistically significant in people with acute tinnitus, and normal hearing and enhancement of DPOAEs was quite frequent.

Turning now to the quantitative comparisons of our study, the results are clearer. The suffering ears of the groups with unilateral tinnitus (i.e. right ears of group R and the left ears of group L) were found to have lower mean values of suppression than the same ears of the control group and of the healthy ears of these groups (right ear of group L and left ear of group R respectively) at almost all frequencies between 1 and 4 kHz using both TEOAEs and DPOAEs. Furthermore, for group B, mean suppression values were significantly lower than the suppression values of the control group. These results show that contralateral suppression amplitudes are generally reduced in tinnitus ears in comparison with normal ears at frequencies of 1–4 kHz with both TEOAEs and DPOAEs. At frequencies of 5 and 6 kHz with DPOAEs no significant results were observed, due to the small number of people who presented contralateral suppression in the control group and due to the fact that the greatest reduction of OAEs normally occurs at frequencies of 1–4 kHz [31,32] after 8 ms, according to studies of the temporal window of TEOAEs [33]. This relates to the MOCS anatomy, which more densely innervates the area of the cochlea at these frequencies [34].

The literature generally supports a reduced suppression of otoacoustic emissions in patients with tinnitus. Lalaki et al. [30] found statistically significant reductions in suppression values in patients with idiopathic tinnitus and noise-induced tinnitus compared to normal subjects. Hsu et al. [35] also showed that suppression of TEOAEs was significantly reduced in tinnitus-positive ears, while suppression of DPOAEs in these same ears was significant only at certain frequencies. Previous studies [36,37] of the CS of OAEs have also indicated alterations in MOCS functioning in groups of tinnitus patients. Nevertheless, there are some studies [21,22] which detected slight differences in the values of CS between tinnitus patients and normal subjects but the numbers did not reach statistically significant levels. In a study by Geven et al. [28], where wavelet analysis of contralateral suppression was used, no differences in suppression between tinnitus patients and the control group were detected at all, and the same negative results were also found by Lind [18]. The diversity of outcomes reflects the variety of the protocols and the range of groups used as well as the different etiologies and hearing status of the tinnitus patients.

Our results indicate an efferent disinhibition in tinnitus patients, pointing to either a reduced response of outer hair cells to MOCS innervation, or to a lesion or impaired activity of the efferent fibers. Although our study was frequency-specific, this dysfunction seems to affect all frequencies between 1 and 4 kHz. Nevertheless, the study by Chery-Croze [39] suggests that the frequency of tinnitus is affected more by efferent disinhibition.

The second part of our experiment concerns the aging of the MOCS in patients with tinnitus. CS values of OAEs seem to be reduced in patients with presbycusis and tinnitus in comparison with people with presbycusis without tinnitus. Nevertheless, these reductions reach statistical significance only in some cases, such as the right ear at 1.4 kHz with DPOAEs and the left ear at 1.4 kHz with DPOAEs and at 2 kHz with both methods. When the mean values of suppression of both ears were compared, only at 2 kHz were the results significant. On the contrary, it was quite interesting that the right and left ears of group P (with presbycusis, without tinnitus) lacked CS less often than the right and left ear of groups R and L (suffering ears) respectively. Moreover, the mean values of suppression of people with presbycusis were higher than the suffering ears of groups with unilateral tinnitus (R and L) at frequencies of 1.4, 2.8, and 4 kHz for the right ear and at 2 kHz for the left ear with both TEOAEs and DPOAEs. Finally, when the mean value of suppression of both ears was compared, the presbycusis group was found to present significantly higher values than the group with bilateral tinnitus (B) at almost all frequencies between 1 and 4 kHz.

When groups with presbycusis without and with tinnitus (P and Q respectively) were compared we would expect significant differences at more frequencies, but this was not possible due to the small number of participants in those groups and to the fact that OAEs and CS are not always present in older people. We can infer that, as in people with tinnitus, patients with presbycusis and tinnitus present lower values of suppression than their control group, though this cannot be proved statistically at every frequency. At the same time, CS is more frequent and presents higher values in people with presbycusis than in people with tinnitus, with sufficient statistical evidence for most frequencies between 1 and 4 kHz. These differences are even more difficult to document at high frequencies (5 and 6 kHz), where almost by definition OAEs are not usually present in people with presbycusis.

It is known that CS declines with age [40], and this reduction, reflecting a MOCS dysfunction, may be the cause of the age-related difficulty of hearing in noise [41]. This decline has been proven to depend more on age than hearing loss [42]. According to Kim et al. [43] this decline mostly affects frequencies of 4–6 kHz, while frequencies of 1–2 kHz seem to be more resistant to ageing of the MOCS. Another study attributed the functional decline of the MOCS to the age-related loss of efferent synapses, without necessarily an age-related loss of outer hair cells [44]. Ozymec et al. [45] showed that the effect of age on DPOAEs is mainly observed in patients with tinnitus and with normal-hearing, rather than in those with tinnitus and hearing loss. Nevertheless, it was shown in our study that age (or the hearing loss due to age) associated with MOCS was less detrimental to its function than the existence of tinnitus in normal hearing patients.

Finally, there is little evidence in the literature about which method (TEOAEs or DPOAEs) better reflects MOCS dysfunction or efferent disinhibition in patients with tinnitus, with or without presbycusis. In the present study, significant differences between TEOAEs and DPOAEs in the amplitude of CS of the groups were rarely observed. Hence, there is no evidence that one method is more sensitive to detect a reduction in suppression values in tinnitus patients. Although DPOAEs can measure suppression even at high frequencies, at least in our experiments this did

not provide statistically significant results, so both methods are equally capable of indicating MOCS dysfunction in patients with tinnitus at frequencies between 1 and 4 kHz.

Conclusions

1. Tinnitus ears present CS less frequently than do normal ones.
2. The CS values in tinnitus ears are significantly lower in comparison with normal ears. Both observations 1 and 2 show a lack of efferent inhibition on the side of tinnitus, so MOCS dysfunction is implicated as a major factor associated with tinnitus generation.
3. MOCS dysfunction can also be seen in patients with tinnitus and presbycusis, although CS values are reduced only at some frequencies.
4. The percentage of presence, and the mean values of CS, were lower in normal-hearing people with tinnitus than in people with presbycusis without tinnitus. Therefore, tinnitus seems to have a more detrimental effect on the MOCS than does presbycusis (regardless of whether the MOCS dysfunction in these patients is due to aging or to the hearing loss itself).
5. Contralateral suppression of TEOAEs and DPOAEs are equally sensitive methods of detecting MOCS dysfunction in patients with tinnitus.

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