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Effect of levodopa on cochlear mechanics and efferent auditory system of Parkinson's disease individuals

Efeito da levodopa na mecânica coclear e no sistema auditivo eferente de indivíduos com doença de Parkinson

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Keywords

Parkinson's Disease
Levodopa
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ABSTRACT

Purpose: To evaluate the effect of levodopa on cochlear dynamics and on the medial olivocochlear efferent pathway of idiopathic Parkinson's disease (PD) individuals. **Methods:** Individuals with and without PD, followed at a University Hospital, were submitted to Distortion Product Otoacoustic Emissions (DPOAE) and DPOAE Inhibitory Effect (OAEIE) in the presence of contralateral noise. Correlation measures between DPOAE and OAEIE results with Hoehn&Yahr (H&Y) stage, daily dose of levodopa and PD diagnosis period were established. Furthermore, electroacoustic measures were compared between individuals without and those with PD, stratified by dose of levodopa daily administered. **Results:** Weak negative correlation between DPOAE amplitude and daily dose of levodopa was found, as well positive correlations between EIEOA with daily dose of levodopa and time of PD diagnosis, respectively. Higher DPOAE amplitude was found in individuals with PD using daily doses of levodopa ≤ 600 milligrams when compared to individuals without PD and those with PD using higher doses. EIEOA was lower in individuals using doses ≤ 600 milligrams, when compared to the other groups. **Conclusion:** Daily doses of levodopa up to 600 mg / day increase the cochlear mechanical-transducer responses in 2 and 3 kHz frequencies, while the action of olivocochlear efferent systems is reduced in this region.

Descritores

Doença de Parkinson
Levodopa
Audição
Vias Auditivas
Dopamina

RESUMO

Objetivo: Analisar o efeito da levodopa na dinâmica coclear, bem como na via eferente olivococlear medial de indivíduos com doença de Parkinson idiopática (DP). **Método:** Indivíduos com e sem DP, acompanhados em um hospital universitário, realizaram a pesquisa das emissões otoacústicas por produto de distorção (EOAPD) e do efeito inibitório das EOAPD (EIEOA) na presença de ruído contralateral. Foram estabelecidas as medidas de correlação entre os resultados das EOAPD e do EIEOA com estágio Hoehn&Yahr (H&Y), dose diária de levodopa e tempo de diagnóstico da DP. Além disso, as medidas eletroacústicas foram comparadas entre os indivíduos sem DP e com DP, estratificados de acordo com a dose de levodopa administrada diariamente. **Resultados:** Foi identificada correlação fraca e negativa entre a amplitude das EOAPD com a dose diária de levodopa e correlações positivas, de força moderada e fraca, entre o EIEOA com a dose diária de levodopa e o tempo de diagnóstico da DP, respectivamente. A amplitude das EOAPD foi maior nos indivíduos com DP em uso de levodopa ≤ 600 miligramas quando comparada à de indivíduos sem DP e com DP, em uso de dose superior. Já o EIEOA foi menor nos indivíduos em uso de doses ≤ 600 miligramas, quando comparado aos demais grupos. **Conclusão:** Doses diárias de levodopa iguais ou inferiores a 600 mg/dia aumentam as respostas mecanotransdutoras cocleares nas frequências de 2 e 3 kHz, enquanto que a ação dos sistemas eferentes olivococleares é reduzida nesta região.

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INTRODUCTION

Idiopathic Parkinson's disease (PD) is a chronic, neurodegenerative disease that presents classic movement disorder symptoms such as tremor, stiffness, bradykinesia and postural instability. The pathophysiology of the disease is related to the degeneration of dopaminergic neurons of the nigrostriatal system and to dopamine depletion[1].

With proven efficacy in the symptomatic improvement of motor aspects, dopamine replacement through oral levodopa administration is still the main pharmacological treatment of clinical choice and can be used alone or as adjunctive therapy to other drugs[2].

Acting as a dopamine precursor, which can transpose the blood-brain barrier, levodopa is decarboxylated in neural tissues, being converted into dopamine, which is stored in presynaptic terminals of striatal neurons[3]. However, with the progression of neuronal degeneration in PD, there is an increase in plasma levels of this neurotransmitter, which is stored in synaptic terminals of other tissues and structures[4]. This condition has been associated to the onset of motor complications in PD due to the chronic use of levodopa, such as fluctuation of motor signal control and dyskinesias[4-6].

Experimental studies with guinea pigs have evidenced the presence of different dopaminergic receptors in afferent and efferent neural auditory pathways, as well as the action of these receptors on the modulatory mechanism of cochlear responses[7-10]. Thus, from these findings, individuals with PD would be expected to present higher frequency of complaints and auditory alterations as a consequence of dopaminergic deficit. However, previous clinical studies have revealed controversial findings regarding the perception of hearing difficulties and the audiometric profile in the disease[11,12].

In this context, it is possible to suppose that dopaminergic replacement performed through oral levodopa administration in individuals with PD can produce effects on the auditory system. Thus, the aim of the present study was to analyze the effect of levodopa on the cochlear dynamics, as well as on the medial olivocochlear efferent pathway of these individuals.

METHODS

The study was performed with individuals diagnosed with idiopathic PD (PD Group), followed between March 2015 and June 2016 in the involuntary movements outpatient clinic of a University Hospital. PD diagnosis was established from the clinical criteria proposed by the Brain Bank of the United Kingdom[13]. A comparison group (Non-PD group) was composed of subjects without PD, users of other outpatient clinics at this hospital, spouses and caregivers of subjects with PD. The composition of this group was established based on the percentage of men and women who composed the PD group, as well as the same percentage of participants in the PD group in each age group.

For both groups, individuals who did not present history of trauma or stroke, history of severe psychiatric disorders and otological diseases, other neurodegenerative diseases, chronic dialytic kidney disease, and congenital hearing loss or diagnosed before the age of 40 years were considered eligible for this study. All individuals who completed audiological procedures were included and those with audiological findings indicative of auditory conduction impairment and with otoacoustic emissions absent in all frequencies surveyed were excluded.

All participants signed a free and informed consent form and the study protocol was approved by the Local Ethics Research Committee (protocol No. 843.890/2014).

In the PD group, the time of disease diagnosis, the daily dose of oral levodopa and the motor stage of the disease according to Hoehn & Yahr (H & Y) were identified. The H & Y stage classifies motor impairment into five stages, considering the presence of tremor, stiffness and bradykinesia unilaterally or bilaterally (stages I and II), onset of postural instability with independence for gait (stage III), aggravation of postural instability depending on aid for displacement (stage IV) and severe disability of movements requiring wheelchair (stage V).

All individuals from the PD group were evaluated during the ON period of the antiparkinsonian medication, that is, when, under the effect of the medication, patients presented reduction in the motor signals characteristic of the disease.

The collection protocol included the performance of air and bone pure tone audiometry (PTA) in an acoustic booth with audiometer model Interacoustic AC40, duly calibrated. Tympanometric curves and acoustic-stapedian reflexes were obtained with AZ7 immittance metering device and the Distortion Product Otoacoustic Emissions (DPOAE) and the DPOAE inhibitory effect (OAEIE) at frequencies 2, 3, 4 and 5 kHz were investigated in acoustic cabinets using the Madsen Accuscreen equipment. DPOAE collection protocol considered the F2 / F1 = 1.24 ratio, with L1 = 60 and L2 = 50 dBNPS and evaluation method by noise-weighted phase statistics.

For the analyses, the measurements of the emission signal (DPOAE signal) and signal / noise ratio (DPOAE S / N) were identified. DPOAE was classified as present when its signal was greater than or equal to -5 dB and the DPOAE S / N was greater than or equal to 6 dB[14]. Considering the influence of the middle ear pressure, DPOAE analysis was performed only in ears with immitance peak in the immitance testing of +50 to -50 daPa.

In the OAEIE survey, white noise in 30 dBNS[15] was used, from the mean of 2 to 4 kHz tonal thresholds, emitted by the AC40 audiometer in contralateral phone to the DPOAE survey. A single search of the DPOAE response was performed in the presence of contralateral noise. OAEIE was calculated by the difference between the measured DPOAE signal without and with noise presentation, considering only the frequencies with the present DPOAE and the magnitude of OAEIE above zero.

The correlation measures between the signal/noise ratio of DPOAE (DPOAE S / N) and OAEIE with the daily dose of levodopa, the PD stage according to H & Y and the time of diagnosis of the disease were estimated.

Additionally, the summary measures of DPOAE S / N and OAEIE obtained in individuals from Non-PD and PD groups were described. In order to identify effects of levodopa on cochlear responses, individuals from the PD group were classified according to the median daily dose of levodopa used, constituting groups PD $\geq$ 600 mg / day and PD <600 mg / day.

Collected data were entered in the Excel software (version 2007) and analyzed in the "R" statistical environment (version 2.11.0). The Pearson Chi-square test was used to compare categorical variables between non-PD and PD groups. For analysis between continuous and / or ordinal variables, Pearson and Spearman correlation tests were used, as well as the unpaired T-student test to compare the means of parameters obtained in the different groups. P <0.05 values were considered as statistical significance.

RESULTS

A total of 47 individuals in the PD group aged 42-84 years with mean age of 63.4 years (± 9.3), of which 33 males (70.21%), were evaluated. The mean time of diagnosis of the disease was 7.7 years (± 6.3), with minimum of 2 months and maximum of 33 years. As for the severity of motor signals, individuals in the early stages of the disease predominate (70.2%), with 13 and 20 individuals with H & Y I and II, respectively, and in more advantaged stages, 10 individuals with H & Y III and 4 individuals with H & Y IV. The mean daily dose of levodopa was 664.4 milligrams (mg) / day (standard deviation 275.7 mg/day) and the median was 600 mg/day.

The non-PD group consisted of 44 individuals aged 42-86 years, with mean age of 64.2 years (± 8.5), with 27 men (61.4%). There was no difference between non-PD and PD groups for the distribution of variables age and sex (p-value = 0.534 and p-value = 0.208, respectively).

The electroacoustic measurements obtained in the right ear were similar to those observed in the left ear. In this way, analyses were performed considering the results of the right and left ears together.

In PTA, individuals from the PD group had 33 ears (35.1%) with thresholds lower than 25 dBHL, 10 ears (10.6%) with only one threshold higher than 25 dBNA and 51 ears (54.25%) with two or more thresholds higher than 25 dBNA, with mean frequencies of 2 to 4 kHz equal to 24.4 dB (standard deviation of 16.35). In the non-PD group, subjects had thresholds lower than 25 dBHL in 27 ears (30.7%); in seven ears (7.9%), only one frequency with threshold greater than 25 dBNA was identified; and, in 54 ears (61.4%), thresholds were higher than 25 dBNA in two or more frequencies, with mean threshold of 2 to 4 kHz equal to 25.7 dB (standard deviation of 16.8).

Table 1 shows the correlation measurements between electroacoustic parameters of the auditory system and clinical conditions of PD. Weak and negative correlations were observed

Table 1. Correlations between electroacoustic parameters of the cochlear auditory system and clinical variables of PD

Auditory parameter	Daily dose of Levodopa (r)	H&Y Stage (rho)	Time of diagnosis (r)
DPOAE S / N			
2 kHz	-0.264	0.108	0.203
(n=63;67%)	p=**0.036**	p=0.383	p=0.100
3 kHz	-0.244	0.024	-0.037
(n=61;64,9%)	p=0.047	p=0.846	p=0.770
4 kHz	-0.127	0.109	0.114
(n=64;68,1%)	p=0.298	p=0.360	p=0.339
5 kHz	-0.102	0.018	-0.027
(n=57;60,6%)	p=0.449	p=0.891	p=0.834
OAEIE			
2 kHz	0.392	0.007	-0.073
(n=52;55,3%)	p=**0.004**	p=0.958	p=0.599
3 kHz	0.424	0.114	0.320
(n=41; 43,6%)	p=**0.005**	p=0.458	p=**0.033**
4 kHz	-0.066	0.099	-0.017
(n=37;39,4%)	p=0.696	0.547	p=0.914
5 kHz	-0.018	0.175	0.079
(n=29;30,8%)	p=0.923	p=0.345	p=0.670

Caption: DPOAE S / N = signal / noise ratio of Distortion Product Otoacoustic Emissions; OAEIE = Otoacoustic Emissions Inhibitory Effect; Statistical analysis through Pearson and Spearman correlations

between the daily dose of levodopa and the signal / noise ratio of DPOAE, indicating that in part of the distribution, increased doses of levodopa lead to a reduction in the amplitude of the signal / noise ratio of DPOAE. The positive correlations identified between dose of levodopa and the magnitude of the inhibitory effect indicate that with increased doses of the medication, there is greater inhibitory action of the efferent system, and this correlation is weak at frequency of 2 kHz and moderate at frequency of 3 kHz.

Analysis of the relationship between levodopa administration and clinical conditions of subjects with PD demonstrated weak and positive correlation between daily dose of levodopa and time of diagnosis (r = 0.212; p-value = 0.044). There was no correlation between H & Y and the daily dose of levodopa (r = -0.032; p-value = 0.764).

Table 2 shows the DPOAE and OAEIE measurements in the non-PD group and in the PD group, being subdivided according to the daily dose of levodopa used. When analyzing the effect of the dose, it was observed that the amplitude of DPOAE is greater in individuals treated with up to 600 mg / day when compared to subjects from Non-PD and PD group> 600 mg / day. On the other hand, measures of the magnitude of the inhibitory effect demonstrate the opposite to what was observed in relation to the amplitude of the signal, and greater responses were found among subjects treated with daily doses greater than 600 mg/day.

DISCUSSION

The results of the present study indicate that the magnitude of DPOAE is greater in individuals with PD who use lower daily doses of levodopa. These findings are consistent with a study that identified an increase in amplitude of DPOAE in new patients after stabilization of antiparkinsonian drug doses[16]. However, our results also demonstrate that this effect of levodopa on the cochlear mechanics does not occur in subjects treated with higher doses of the drug.

The amplitude of DPOAE is a parameter that reflects the amount of sound energy produced by the contractile capacity of external hair cells (EHC). This contractile activity is the main mechanism responsible for the selective amplification of the basilar membrane, promoting cochlear tonotopic stimulation[17]. In addition, evidence from experimental animal studies[9,10] points to the action of D2 dopaminergic receptors on the functioning of EHC, acting on the amplitude of DPOAE and cochlear microphonism.

It is known that at the beginning of dopaminergic replacement in PD, there is a significant improvement of motor symptoms, since levodopa is metabolized into dopamine and is stored in the terminals of the remaining striatal dopaminergic neurons[5]. When released by these terminals, dopamine acts by mediating the antiparkinsonian action of levodopa, stimulating postsynaptic

Table 2. Electroacoustic measures (in decibels) obtained in Non-PD and PD groups, stratified according to the daily dose of levodopa

Procedures	Non-PD (n=88)		PD Levodopa ≤ 600 (n=52)		p-value	PD Levodopa > 600 (n=42)		p-value
	Mean	sd	Mean	sd		Mean	sd	
DPOAE S / N								
2 kHz	14.4	1.6	15.2	1.1	**0.006**[a]	14.5	1.7	0.921[b]
	(n=55;62.5%)		(n=32;61.5%)			(n=31;73.8%)		**0.043**[c]
3 kHz	14.1	1.4	14.9	1.5	**0.021**[a]	14.5	1.4	0.227[b]
	(n=54;61.4%)		(n=31;59.6%)			(n=30;71.4%)		0.258[c]
4 kHz	14.5	1.5	14.8	1.7	0.292[a]	14.4	1.6	0.664[b]
	(n=63;71.6%)		(n=35;67.3%)			(n=34;80.9%)		0.333[c]
5 kHz	15.1	1.3	15.4	1.3	0.350[a]	15.1	1.3	0.846[b]
	(n=54;61.4%)		(n=27;51.9%)			(n=30;71.4%)		0.637[c]
OAEIE								
2 kHz	2.9	2.3	1.9	1.6	**0.049**[a]	4.1	3.9	0.218[b]
	(n=35;39.8%)		(n=26;50%)			(n=26;61.9%)		**0.011**[c]
3 kHz	1.92	1.3	1.54	1.39	0.356[a]	3.2	3.1	0.087[b]
	(n=36;40.9%)		(n=17;32.7%)			(n=24;57.1%)		**0.016**[c]
4 kHz	2.28	2.66	3.4	4.1	0.290[a]	1.9	1.7	0.876[b]
	(n=37;42%)		(n=18;34.6%)			(n=19;45.2%)		0.085[c]
5 kHz	1.99	2.88	2.41	4.42	0.756[a]	0.3	1.9	0.740[b]
	(n=29;32.9%)		(n=13; 25%)			(n=16;38.1%)		0.683[c]

Caption: DPOAE S / N = signal / noise ratio of Distortion Product Otoacoustic Emissions; OAEIE = Otoacoustic Emissions Inhibitory Effect; [a]Non-PD group PD Levodopa dose ≤ 600 mg / day; [b]non-PD group PD> levodopa dose> 600 mg / day; [c]PD group levodopa dose ≤ 600 mg / day × PD levodopa dose> 600 mg / day. Statistical analysis using unpaired Student's t-test

dopaminergic receptors[3]. However, the association between chronic levodopa administration and motor complications, such as levodopa-induced fluctuations and dyskinesias[4,7], occurring in 40% to 50% of cases after four to six years of treatment[9].

The motor complications in PD, due to the continuous use of levodopa, do not yet have their pathophysiology well understood. However, its mechanism seems to be related to the progressive degeneration of dopaminergic neurons in the disease, which implies problems in the mechanism of dopamine decarboxylation and deficits in the storage and reuptake of this neurotransmitter in the synaptic vesicles[4].

Considering the mechanism that metabolizes levodopa into dopamine, it is possible to suppose that dopamine levels in the cochlea are elevated in individuals treated with lower doses, supposedly also with shorter disease time, promoting greater action of dopaminergic receptors on the micromechanical transduction activity of EHC. On the other hand, the relationship between increased doses of levodopa and reduced dopamine storage and release in synaptic terminals leads to the hypothesis that there is a reduction in dopamine levels in subjects treated with more than 600 mg / day of levodopa, showing a reduction in cochlear dopamine levels, leading to a decrease in the electromotility of EHC.

Interestingly, our results also show that in subjects with PD who use lower daily doses of levodopa, there is a lower inhibitory effect of cochlear responses at frequency of 2 kHz, while in those with higher doses, this effect is higher at frequencies of 2 and 3 kHz. No studies that have observed responses of the olivocochlear efferent system in PD were found. However, OAEIE is known to reflect the functioning of the medial olivocochlear efferent system (MOES), which inhibits EHC contractile responses in the presence of competitive noise[18] and its activity mediated by cholinergic and gabaergic neurotransmitters[19]. On the other hand, cochlear responses are also influenced by the lateral olivocochlear efferent system (LOES), which has dopamine as one of its main neurotransmitters[19].

LOES acts on synaptic terminals of internal hair cells (IHC) in communication with fibers of the cochlear nerve, reducing the action potential and summation of these fibers[19]. This system reduces the neurocochlear activity, acting against the excitotoxic mechanism of glutamate in synaptic terminals through the release of dopamine[20]. With the increase of dopamine release, through a neuromodulatory loop, there will be inhibition of glutamatergic receptors and increase of gamma-aminobutyric acid (GABA), which, in turn, will act by reducing dopaminergic release[19].

Considering the mechanism described above, it is possible that high doses of intracochlear dopamine, as inferred by increasing the amplitude of DPOAE in subjects with reduced doses of levodopa, promote the triggering of this neuromodulatory loop, reducing the action of glutamate on the synaptic terminals of IHC. Thus, there would be an increase in the membrane potential of cochlear nerve fibers, impairing the transmission of the suppressor stimulus (contralateral white noise) in the OAEIE research of these individuals. The decrease in intraocular dopamine, corroborated by the lower amplitude of DPOAE in subjects treated with high doses of levodopa would increase the excitatory power of glutamate in the auditory pathways, triggering a more expressive response to LOES and also increasing the inhibitory effect of MOES.

These hypotheses are corroborated by an experimental study with animals[7] that demonstrated the action of transcripts related to glutamatergic neurotransmission in the cortical-thalamic-olivary pathways through a complex regulation of excitatory and inhibitory receptors in the control of cochlear mechanics.

Considering the above, the findings of the present study point in the direction that, even if there is no direct effect of dopamine on MOES, the inhibitory effect of the cochlear efferent system, at some level, would undergo an overregulation due to the action of LOES in subjects with PD who undergo dopaminergic levodopa replacement.

Additionally, it was possible to verify that, in our study, the time of diagnosis is associated with the highest OAEIE, leading us to believe that this association is due to the effect on levodopa on the efferent mechanism of cochlear control, since the time of diagnosis positively correlates with higher doses of levodopa.

At first, it would be plausible to consider the influence of the motor stage on the cochlear responses observed in our study. However, it should be observed that none of the parameters of the cochlear function analyzed correlated with the motor stage of PD, which was not associated with the use of higher doses of levodopa. Thus, these findings lead us to refute this influence, allowing us inferring that the differences found in the amplitude of DPOAE and OAEIE between PD and non-PD groups are due to levodopa administration.

The results found present important evidence related to the action of dopaminergic replacement in cochlear activity. However, it is imperative that the hypotheses raised are proven, since they constitute an initial step in the analysis of auditory dopaminergic pathways in a clinical model of investigation in individuals with PD.

Among the limitations of the present study, the potentially insufficient intensity of the stimulus to investigate the inhibitory effect at higher frequencies stands out, considering the presence of hearing loss at frequencies of 4 and 6kHz. In addition, the results should be interpreted with caution, as no other exposures that could interfere with the outcome were considered. Thus, further studies should investigate the effect of other drugs used to treat the disease, as well as the analysis of cochlear responses in new cases of PD in order to minimize the effects of chronic use of levodopa in the body of parkinsonians and interactions of medicines used as adjunctive therapy for the symptomatic treatment of PD. In addition, a detailed analysis related to the participants' noise exposure history may contribute to experimental studies that point to the protective effect of dopamine on cochlear structures under hypoxicemic conditions.

CONCLUSION

Dopaminergic replacement performed by the administration of its precursor, levodopa, presents differentiated effects on cochlear responses and on the olivocochlear efferent system of individuals with Parkinson's disease, depending on the daily dose administered and the cochlear tonotope region. Daily doses of levodopa equal to or less than 600 mg / day increase

cochlear mechanical transducer responses at 2 and 3 kHz frequencies, while the action of olivocochlear efferent systems is reduced in this region. Thus, the present study contributes to a better understanding of the functionality of dopaminergic cortical-olivocochlear pathways from clinical findings in humans.

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Author contributions

MSL and APC participated in work planning and design and in all stages of conducting the research and construction of the manuscript, as well as in its final review; ASM collaborated with the general review of the manuscript; ACN participated in the work design and collaborated in the final review of the manuscript.