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Role of melatonin in the prevention of noise-induced hearing loss - CILcare-Agropolis Science Park

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Introduction

Age-related hearing loss (ARHL) is an irreversible neurosensory disorder characterized by decreased hearing threshold sensitivity and speech comprehension skills. This condition generally arises during the fourth decade of life with progressive worsening with age. It affects approximately 25–40% of people over the age of 65 and 80% of these over 85. Some studies have shown an association between ARHL and depression, gait difficulties and cognitive decline.

ARHL is a multifactorial (environmental and genetic) condition that involves both cochlear hair cells and neurons and can cause cell degeneration in the stria vascularis [4,6–8]. Throughout life, the most common and irreversible aging effect on the auditory system is the death of cochlear hair cells, which usually occurs by apoptosis in response to oxidative stress. A recurrent complaint of senile individuals is difficulty with speech comprehension, especially in noisy environments.

Antioxidant substances have potential for the prevention or delay of epithelial cell death and are the topic of recent studies on deafness and aging. Among these substances, melatonin (N-acetyl-5-methoxytryptamine) has shown therapeutic promise. Melatonin originates from serotonin, and is the primary hormone of the pineal gland, where it is synthesized by pinealocytes with tryptophan as its main precursor. Melatonin is also synthesized locally in extrapineal tissues and organs. It stimulates the assembly of varied enzymes that protect cells, lipids, proteins and DNA from oxidative damage and crosses many morphophysiological barriers, increasing its cross-tissue effectiveness in neutralizing reactive oxygen species. Due to these antioxidant characteristics, melatonin has already shown promise within the field of aging, where numerous studies have investigated the role of melatonin on different cellular mechanisms associated with aging

Melatonin has been shown to be effective in the prophylaxis of cochlear damage caused by noise [20] as well as in improving the ototoxicity caused by cisplatin .As age increases, melatonin production decreases, depriving the body of 1 of its most potent antioxidant compounds, which can favor the emergence of ARHL.

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Aims

To evaluate the effect of melatonin on the prevention of HCD dysfunction within the ARHL process during a susceptible murine C57BL/6J model.

Abstract

Melatonin is a hormone produced by the pineal gland in animals that regulates sleep and wakefulness. It is involved in the circadian rhythms synchronization including sleep-wake timing, blood pressure regulation, seasonal reproduction, etc.

However other physiological roles have been described for melatonin such as antioxidant protection of nuclear and mitochondrial DNA, anti-inflammatory effect by TNF-α inhibition, etc.

Because increasing number of studies demonstrated that antioxidants may serve as effective compounds to block cochlear inflammation and hair cells apoptosis, targeting members of antioxidant pathways could be feasible options for the treatment of several types of hearing loss. For this reason, the aim of this study is to determine the effect of melatonin in the hearing impairment and anxiety induced by acoustic trauma.

After completion of data collection at 15 months of age, the animals were sacrificed by placing them in a hermetically sealed box containing a transparent display with a CO2 concentration maintained at 40%. Death of the animal was confirmed by the absence of corneal reflex and heartbeMaterial and methods

Type of study and animals

This was an experimental, prospective and interventional study of 32 male C57BL/6J mice acquired from the vivarium at the University of Campinas (UNICAMP).

The animals were obtained when they were four weeks old and were housed in the vivarium of the University of Brasilia for another four weeks of adaptation. During this time, the mean room temperature was 25±3°C, natural sleep and wake cycles were induced, and mice were housed in environmentally enriched cages with access to water and balanced feed ad libitum.

After the adaptation period, animals were kept at the same vivarium and were handled according to the rules of the Brazilian College of Animal.

Study and treatment groups

The animals were evaluated using otoscopy. Animals presenting signs of otitis externa, acute otitis media or a meatus too narrow to adequately accommodate the probe of the otoacoustic emission equipment were removed from the study. The animals were then submitted to auditory screening using a distortion product otoacoustic emissions (DPOAE) apparatus (ERO-SCAN®—MAICO Diagnostics) in an acoustically isolated cabin under anesthesia with 65 mg/kg ketamine hydrochloride and 6.5 mg/kg xylazine. The animals showing the presence of DPOAEs in at least one ear were used in the experiment. The animals were divided into two groups:

Control group (CG, n = 16), receiving 50 µl/day of saline and ethanol (12%), orally

Melatonin group (MG, n = 16), receiving 10 mg/kg/day of melatonin (Sigma Aldrich®, St Louis, United States) diluted in 12% of ethanol, orally

Daily, each animal received by oral gavage a total volume of 50 µl administered through an

automaticpipette. Both groups were supervised daily during the 10-month study period.

Experimental procedure

Otoacoustic emissions were measured at the beginning of treatment and each month at 6, 8, 10 and 12 kHz. The function of outer cochlear hair cells was determined by DPOAE using an ERO-SCAN (MAICO Diagnostics). For the test, the animals were anesthetized with ketamine hydrochloride and xylazine, as described above. Before the recording of evoked otoacoustic emissions (EOAE), the animals were submitted to manual otoscopy for the evaluation of the auditory meatus and the tympanic membrane, and those presenting signs of otitis or earwax of difficult removal were excluded from the test. The DPOAE test was performed before treatment and immediately before sacrifice, using the 2f1-f2 frequency with an f1/f2 ratio of 1.22, presented at an average intensity of 65dB SPL for f1 and 55dB SPL for f2. The emission values obtained in the CG were considered as a reference for this strain. Acoustic signals registered on the external acoustic meatus were cochlear responses that aged mice are especially sensitive to. Therefore, DPOAE measurement is a reliable method for ARHL-related studies, since the acoustic signals recorded in the external auditory canal are considered cochlear responses to frequencies that are altered by aging.

Statistical analysis

The normality of the distribution of variables was analyzed by the Kolmogorov-Smirnov test, while the variability of variances was analyzed by Bartlett's test. ANOVA followed by the Student-Newman-Keuls or Kruskal-Wallis followed by the Dunn test were used to compare multiple parametric or non-parametric samples, respectively. Student's t-test or the Mann-Whitney test were used to compare two independent normal or non-normal samples, respectively. Linear regression was used to evaluate the monthly DPOAE behavior.

The Prism Software Package program (GraphPad, USA, 2005) was used for performing the statistical tests and for graphical representations. Values of $p<0.05$ were considered statistically significant.

Results

There was a decrease in DPOAE values in both groups over time and a differentiation between them from the 10th month of life onwards. At 10 months, the MG maintained higher DPOAE values than the CG in the least frequencies tested.

Conclusion

The use of melatonin has otoprotective effects on HCD within the ARHL process within the C57BL/6J model.