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Does systemic steroid deficiency affect inner ear functions?☆

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ABSTRACT

Purpose: Today corticosteroids are employed for the treatment of various inner ear disorders. In this study we have investigated probable changes in hearing functions resulting from a deficiency of systemic steroid secretions.

Materials and methods: Twenty four healthy female rats were used in our study, allocated into three groups (medical adrenalectomy, medical adrenalectomy + dexamethasone, no treatment). Audiological evaluations were conducted at the beginning of the study and on days 7, 14 and 21. Blood samples were taken at the beginning and at the end of the study and blood corticosterone levels were determined.

Results: While there were no significant differences between the basal, 7th, 14th and 21st day DPOAE values of group 1, their ABR threshold values showed significant increases. In group 2, there were no significant differences between the basal, 7th, 14th and 21st day DPOAE values. ABR thresholds of group 2 showed significant increases on days 7 and 14 as compared to their basal values, but there were no significant differences between the 21st day and basal ABR threshold values. There were no significant differences between the basal cortisol levels of the three groups. The mean cortisol level of group 1 on day 21 was found to be significantly lower than those of groups 2 and 3.

Conclusion: The results of the study demonstrated that there were no significant changes in DPOAE values with the cessation of cortisol secretion, while there was a progressive increase in ABR thresholds, which could be overcome with cortisone replacement.

1. Introduction

Cortisol is a steroid hormone secreted by the adrenal cortex. Presently it is widely used due to its anti-inflammatory, anti-allergic and immunosuppressive effects. It is administered both systemically and topically in otolaryngological practice.

The effects of corticosteroids on the inner ear have been reported to increase anti-ROS enzyme activity in the cochlea, to decrease inflammatory molecule formation, and to reduce

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inner cell apoptosis induced by ototoxicity [1–4]. Steroids are used for treating various ear pathologies such as sudden sensorineural hearing loss, hearing loss due to noise exposure, Meniere's disease, salicylate and aminoglycoside ototoxicity [1,2,5].

Various studies demonstrated the presence of a substantial amount of corticosteroid receptors on inner and outer hair cells, on spiral ganglion neurons and the spiral ligament [6–8]. The preferred steroid for ear pathologies has almost always been dexamethasone, since it is one of the most potent and longest acting corticosteroids, causing the least sodium retention, with no untoward effects on cochlear functions [9,10]. The objective for steroid use is to reduce immunity induced inflammation resulting in autoimmune dysfunction, or to revert the pathology by directly affecting the inner ear neuroepithelium [11]. Previously, steroids were being administered only systemically for ear pathologies, but once their effects were well confirmed, intratympanic steroid administration came to be practiced for augmenting the drug's effect on the inner ear and for delivering higher doses. Various studies have demonstrated the successful results of intratympanic steroid use, especially for dexamethasone [12–15].

Relying on the above information steroids are thought to have a role in the reversal of ear pathologies. Since steroid administration may bring forth recovery from ear pathologies, there may as well be a relationship between hearing functions and systemic steroid levels. There is only limited information in medical literature on this subject. In our study we aimed to investigate the probable effect of steroids secreted from the adrenal gland on hearing functions and whether hearing functions were affected when the adrenals stopped secreting steroids. Thus the secretion of steroids from the adrenal gland was inhibited by aminoglutethimide, an agent which induced chemical adrenalectomy, and hearing functions were evaluated by audiological measurement.

2. Materials and methods

2.1. Animals and groups

After the approval of the Animal Research Local Ethics Committee, 27 healthy female Wistar Albino rats (200–240 g) were included in the study. Rats with a positive Preyer reflex were chosen, endoscopic ear examinations were conducted, and any rat with an outer or middle ear pathology was excluded from the study group. Rats were kept in an environment which was illuminated for 12 hours and darkened for 12 hours and had a temperature of 21 ±1 °C, with free access to food and water, and with a background noise below 50 dB. The animals were used in accordance with the Guide for the Care and Use of Laboratory Animals [16].

Group 1 (medical adrenalectomy) (n = 10): Aminoglutethimide 400 mg/kg/day (i.p.) 21 days.
Group 2 (medical adrenalectomy + dexamethasone) (n = 10): Aminoglutethimide 400 mg/kg/day (i.p.) + dexamethasone phosphate 5 mg/kg/day (p.o.) 21 days.
Group 3 (control) (n = 7): Saline 5 mg/kg/day, p.o. 21 days.

2.2. Aminoglutethimide

Aminoglutethimide blocks the main route of cortisol biosynthesis from cholesterol, by inhibiting the CYP11A1 enzyme. It has been demonstrated that there was a significant decrease in plasma corticosteroid levels of rats at the end of 28 hours after being administered 400 mg/kg of aminoglutethimide, as compared to the control group which were given saline only [17]. Also, the plasma corticosterone level of the group which was given aminoglutethimide + dexamethasone phosphate was significantly higher than that of the group which was given aminoglutethimide only, but was significantly lower than the control group [17]. Spanwick et al. have shown that when 1 mg cortisone was administered to adrenalectomized rats, their daily cortisone levels were the same as rats with intact adrenals [18]. In light of the above information, we decided to use aminoglutethimide in our study in performing chemical adrenalectomy.

2.3. Audiological evaluation

2.3.1. DPOAE

The GSI Audera device was used for DPOAE measurements in evaluating the animals' peripheral hearing. The smallest size elastic tympanometry probe was used for the rats. Emissions were performed in General Diagnostic mode, and both DPgram and input-output (I/O) measurements were taken. Otoacoustic emissions were measured using stimuli in different frequencies and intensities. Primary stimulus intensities were adjusted to 65 dB (L1 = L2). The two different frequencies (f1 and f2) were set as f2/f1 = 1.10. The DPgram measurements were performed at 3000, 4008, 5004, 6000, 6996, 8004, 9012, 10008, 11004 and 12000 Hz. frequencies. During measurements, DPOAEs with a noise intensity of 3 dB and over at 2f1-f2 frequency were accepted as positive.

2.3.2. ABR

ABR measurements were conducted in a silent room with the Viasys Medelec Synergy device, using subdermal needle electrodes (Technomed Europe). ER 3A insert earphones were used to provide click stimuli in alternating polarities. Filter was set at 30–1500 Hz, repetition rate was set at 21/s, and the time window was set at 25 ms. 1024 samples were taken for signal averaging. Initially stimuli were presented at 80 dB nHL intensity, and the intensity level was reduced in 20 dB steps until close to the threshold value. Then the intensity level was reduced in 10 dB steps until threshold value was reached. At least 2 tracks were generated for each measurement to test behavior reproducibility, and the threshold was cross checked. The ABR threshold was defined as the lowest intensity level where the III wave was observed.

2.4. Biochemical evaluation

Samples were taken and stored at −80 °C until the day of measurement. The concentrations of rat cortisol in serum were calculated with enzyme linked immunosorbent assay (ELISA) kit, according to protocols provided by manufacturers (EASTBIOPHARM; lot no: 20130412; PRC). Multiskan FC® Microplate Photometer (Thermo Scientific; United States) was used for reading at 450 nm. The results were expressed in ng/ml.