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The protective effect of adrenocorticotropic hormone treatment against noise-induced hearing loss☆

Ahmet Mutlu [a,*], Fatma Ceyda Akin Ocal [b], Seyra Erbek [c], Levent Ozluoglu [c]

[a] Uskudar State Hospital, Otorhinolaryngology Department, Istanbul, Turkey
[b] Gulhane Training and Research Hospital, Otorhinolaryngology Department, Ankara, Turkey
[c] Baskent University Medical Faculty, Otorhinolaryngology Department, Ankara, Turkey

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ABSTRACT

Objective: NIHL is a common problem, and steroids are the most effective treatment option. In this study, we aimed to evaluate the protective effects of the synthetic adrenocorticotropic hormone (ACTH) analogues, which induce endogenous steroid secretion, against noise-induced hearing loss (NIHL) and to compare their effectiveness with that of steroid treatment.

Methods: Twenty-four male Sprague–Dawley albino rats were divided into four subgroups as follows: group 1 (n = 6) control, group 2 (n = 6) saline, group 3 (n = 6) dexamethasone (2 mg/kg/day intramuscularly [IM]), group 4 (n = 6) ACTH analogue (0,4 mg/kg/day IM), respectively. Three groups (groups 2–4) were exposed to white noise (105 dB SPL, 12 h). All the rats were evaluated for hearing thresholds of 10 kHz, 20 kHz, and 32 kHz via acoustic brainstem responses (ABR) measurement. After the basal threshold measurements, measurements were repeated immediately after the noise and on day 7 and day 21.

Results: Both steroid and ACTH analogue groups showed significantly better hearing outcomes than the saline group on day 7 ($p < 0.001$) and day 21 ($p < 0.001$) after the noise exposure. No superior treatment effect was demonstrated in either the steroid or ACTH analogue group. None of the related intervention groups reached the basal hearing thresholds.

Conclusion: Steroids were effective drugs for the treatment of NIHL. ACTH analogues also demonstrated promising therapeutic effects for NIHL. Further studies to establish ACTH analogues as an alternative NIHL treatment option to steroids are needed.

1. Introduction

Noise-induced hearing loss (NIHL) is an ear injury, which can occur via the exposure of a sudden or prolonged high-decibel noise. It has become a common problem in the modern population [1]. The intense sound may cause temporary or permanent hearing threshold shift with the macroscopic (tympanic membrane rupture, ossicular chain dislocation, perilymph fistula, etc.) and microscopic (tectorial and basilar membrane rupture, hair cell loss, etc.) effects in the ear [2]. Besides, the related effects stimulate the metabolic cell responses to maintain the cell homeostasis. Paradoxically, the related metabolic activity might also disrupt the vital cochlear structures and in turn cause apoptosis, which is relevant to permanent hearing loss. For this reason, many studies have aimed to find an effective treatment to treat NIHL. However, the suggested treatments for NIHL do not recommend a specific treatment, except for

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* Corresponding author at: Barbaros Mahallesi, Veysi Pasa Sokak No:14, 34672 Uskudar, Istanbul, Turkey.
E-mail addresses: ahmutlu1988@gmail.com (A. Mutlu), (F.C.A. Ocal), (S. Erbek), (L. Ozluoglu).

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the use of steroids [1]. Recent studies have revealed the promising effects of the glucocorticoids, which have been widely used against NIHL [1–3].

Glucocorticoids are lipophilic hormones, which are synthesized from cholesterol precursors and strongly associated with maintaining homeostasis during stress-related events (e.g., trauma, infection, hypoglycemia, physical stress, and exercise) [3,4]. Glucocorticoids are also released from the adrenal glands according to the diurnal rhythm, and secretion is controlled by the adrenocorticotropic hormone (ACTH) as a part of the hypothalamic-pituitary-adrenal axis.

ACTH is a polypeptide hormone, which is produced by cells of the anterior pituitary gland. It stimulates the secretion of corticosteroid hormone (i.e., glucocorticoid, aldosterone) from the adrenal glands and can be eliminated in minutes [3]. The synthetic ACTH analogues are manufactured with the aim of enhancing the blood elimination period for therapeutic applications. Currently, the synthetic ACTH analogues are generally preferred as a drug to demonstrate the endogenous glucocorticoid secretion from the adrenal gland (ACTH stimulation test) and West syndrome; in fact, it may be an alternative option to steroid treatment for exacerbations of multiple sclerosis and ulcerative colitis, rheumatoid arthritis, and psoriatic arthritis [5]. The promising effects of the ACTH analogues may shed light on new treatment protocols for different disorders.

The aim of this present study was to evaluate the protective effects of the synthetic ACTH analogues against NIHL. The protective effects of the ACTH analogues against NIHL were also compared with the effects of dexamethasone, which is a potent steroid. To our knowledge, this study represents the first preliminary study aimed to evaluate the synthetic ACTH analogue effects on NIHL.

2. Methods

2.1. Animals and experimental design

This study was conducted in the Baskent University Medical Faculty animal laboratory under the statement of the local ethic committee (Project Number: DA16/47). Twenty-four male Sprague–Dawley albino rats aged 12–16 weeks and weighing 280 g–320 g were included in this study. The rats were maintained under standardized laboratory conditions (12-h light/dark cycle, temperature 21 ± 1 °C, background noise <50 dB) with access to food (standard rodent chow) and water ad libitum.

Ear examinations and hearing tests were performed under general anaesthesia with a mixture of ketamine (60 mg/kg intraperitoneal [IP]) and xylazine (6 mg/kg IP). Before the hearing tests, all the rats were examined with an otoscope and controlled for normal external ear canal with an intact tympanic membrane.

Twenty-four rats were divided randomly into four groups of six rats per cage. The groups and respective interventions are summarized in Table 1 and as follows.

- Group 1 (n = 6): This group was classified as the control group. The rats in this group did not receive acoustic trauma and were not administered drugs.
- Group 2 (AT + Sal) (n = 6): This group was classified as the saline group. The rats in this group received the acoustic trauma and saline injections (0.2 mL/day intramuscularly [IM] 7 days after the acoustic trauma).
- Group 3 (AT + Dex) (n = 6): This group was classified as the dexamethasone group. The rats received the acoustic trauma and dexamethasone injections (2 mg/kg/day IM 7 days after the acoustic trauma) [6].
- Group 4 (AT + ACTH) (n = 6): This group was classified as the ACTH group. The rats received the acoustic trauma and synthetic ACTH analogue injections (Synacthen Depot®, 0.4 mg/kg/day IM 7 days after the acoustic trauma) [7].

2.2. Acoustic trauma model

After the basal trauma, all the rats (except group 1) were placed in a quiet cabin (403-A, Industrial Acoustics Company® GMBH, Germany). The cages were located 50 cm away between two free-field loudspeakers. The acoustic trauma (white noise 105 dB SPL, 12 h) was generated with a calibrated clinical audiometer device (AC 40 Interacoustics®, Denmark).

2.3. Hearing tests

The auditory brainstem responses (ABR) was recorded using the Smart EP high frequency device (Intelligent Hearing System-IHS®, Miami, FL, USA) fitted with high-frequency transducers and measurement were performed with the official software (version 5.30). ABR waves were recorded with subdermal needle electrodes, which are placed in the vertex (active), below the ipsilateral pinna (reference), and below the counter-lateral pinna (neutral). The electrode impedance was set to 0–3 kOhm and was connected to a 0.1 kHz–3 kHz preamplifier filter.

The acoustic stimuli were presented with insert earphones, and three different (10 kHz, 20 kHz, and 32 kHz) tone burst frequencies (rarefaction polarity) were selected [8]. The tone burst acoustic stimuli rate was set as 21.1/s (1562 μs in duration; cos2-shaped; 21 Hz) with 0.1–3 kHz band pass filter [2]. The average sweep number for each stimulus was set to 2000 sweeps. The evaluation of the hearing thresholds was started from the 80-dB intensity, and the wave II of the ABR patterns were used to define the thresholds. 20-dB decrements and 10-dB increments were used to distinguish the lowest intensity levels of the ABR wave patterns. All the measurements were repeated to obtain the exact thresholds via two investigators.

After the basal level measurements, three groups received the acoustic trauma. The measurements were repeated immediately in all groups to evaluate the effectiveness of the acoustic trauma (control group was also assessed to screen the measurement). The treatment success was evaluated by revisiting the measurements in all groups on day 7 and day 21 of the acoustic trauma.

2.4. Statistical analysis

All the statistical data were assessed using SPSS software (version 16.0, SPSS, Inc., Chicago, IL, USA). Descriptive

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