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Original Article

# Electrophysiological Effects of Intratympanic Retinoic Acid Application Following Acoustic Trauma in Rats

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**BACKGROUND:** Retinoic acid (RA), the active metabolite of vitamin A, is essential for the embryonic development of the inner ear, involving processes such as cell proliferation, differentiation, and morphogenesis. It also plays a crucial role in the protection and maintenance of the inner ear during the postnatal period. This study investigated the electrophysiological effects of early intratympanic RA administration following acoustic trauma.

**METHODS:** Two doses of intratympanic RA injections were administered to 21 Sprague–Dawley rats after acoustic trauma, and the distortion product otoacoustic emissions of all rats were measured after RA injections.

**RESULTS:** After Noise-Induced Hearing Loss, 2 doses of RA were administered intratympanically, and significant differences were found in signal-to-noise ratio (SNR) values at 1, 1.4, 2, 2.8, 4, 6, and 8 kHz frequencies after RA injections ($P < .001$). In addition, SNR also increased after each RA dose at frequencies of 1.4, 2, 2.8, 6, and 8 kHz ($P < .05$).

**CONCLUSION:** Due to the advancing industry and technology, noise exposure and the resulting hearing loss have become common issues today, and absolute and effective agents for treatment have not yet been achieved. This study found that intratympanic RA injections administered after acoustic trauma have a protective effect against acoustic trauma. However, these results should be supported by further research in humans.

**KEYWORDS:** Acoustic trauma, evoked potentials, intratympanic injection, noise induced hearing loss, otoacoustic emission, otology, retinoic acid

## INTRODUCTION

Hearing loss is a widespread sensory impairment, second only to mental disabilities, and is increasing. Early detection and prevention can enhance care, access, and quality of life. High noise exposure in industrial societies leads to around 1.6 million new cases of hearing loss annually, with the WHO estimating that one billion people aged 12-35 are at risk of noise-induced hearing loss (NIHL).[1]

Loud noise can damage the stiffness of outer hair cells (OHCs), but rest can aid recovery.[2] Continued exposure risks irreversible harm to stereocilia, leading to sensory hair cell death and sensorineural hearing loss, along with structural changes like the collapse of the Organ of Corti.[3]

In NIHL, damage occurs through mechanical means, such as hair cell loss, and biochemical means that increase oxidative stress and harm mitochondria.[4] While mechanical damage stops after exposure, biochemical damage can last 7-10 days,[5] suggesting that antioxidant treatments during this time may support recovery.[6]

Signal processing between inner hair cells (IHCs) and type I spiral ganglion neurons relies on calcium-triggered glutamate release, making postsynaptic terminals vulnerable to noise-induced excitotoxicity.[7] Mild noise exposure can damage synaptic connections, leading to cochlear synaptopathy, hidden hearing loss, tinnitus, and cognitive issues.[8,9]

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Since excessive reactive oxygen species (ROS) generation is a major factor in noise-induced cochlear damage, typical therapeutic approaches involve neutralizing or suppressing ROS production through antioxidant supplements.[4,5]

The treatment goals for NIHL include:

1) Reducing lipid peroxidation in the organ of Corti,
2) Ensuring proper cochlear blood flow during and after noise exposure,
3) Inhibiting apoptotic pathways to protect hair cells.

Local treatment of hearing loss involves various agents, including glucocorticoids, growth factors, and antioxidants, requiring knowledge of inner ear pharmacokinetics. One method of intratympanic administration is transtympanic injection with a 28-gauge dental needle.

In this experimental animal study, in line with previous research, an acoustic trauma model was created on 21 rats by exposing them to 4 kHz at 110 dB SPL for 12 hours. This was confirmed through otoacoustic emission (OAE) measurements taken just before and after the trauma. Consistent with the literature, the study identified damage to the OHCs through distortion product otoacoustic emissions (DPOAE) testing after the acoustic trauma. A RA solution was then administered intratympanically at the first hour post-trauma and again 48 hours later. Subsequent DPOAE testing revealed a significant change in the group treated with RA.

Many small molecules and drugs with a protective role have been identified in the treatment of NIHL, aiming to understand the roles of mechanical and biochemical damage in the cochlea.

In conclusion, if necrosis and apoptosis are major contributors to cochlear damage mechanisms, it is believed that agents inhibiting apoptosis and necrotic cell death could also mitigate noise-induced damage.

The recognition of free oxygen radicals and mitochondrial damage has prompted the use of antioxidants like Coenzyme Q10, Idebenone, and N-acetyl-cysteine. These compounds reduce apoptosis post-noise exposure, enhancing hearing thresholds.[10] Intrinsic antioxidants such as glutathione and ebselen are produced by the body,[11,12] while exogenous sources include resveratrol, vitamin C, and D-methionine.[13]

## MAIN POINTS

- Intratympanic retinoic acid (RA) administration was investigated for its electrophysiological effects following acoustic trauma in rats.
- Significant improvements in signal-to-noise ratio (SNR) values were observed at multiple frequencies after RA injections.
- Two doses of RA resulted in a statistically significant increase in SNR at 1.4, 2, 2.8, 6, and 8 kHz.
- The findings suggest that RA may protect against noise-induced hearing loss.
- Further research in human studies is needed to validate the potential therapeutic benefits of RA.

Vitamin A is a fat-soluble vitamin derived from carotenoids, converting into active forms like retinol and RA.[17] While natural retinoids are found at low levels in the bloodstream, synthetic retinoids are used to treat skin disorders such as psoriasis.[10]

Retinoids are crucial for gene regulation and cellular development.[10,14] A deficiency in RA in the middle ear can increase noise sensitivity, and insufficient vitamin A raises the risk of acoustic trauma in the inner ear. Early treatment with RA after noise exposure can reduce hair cell loss.[15]

Retinoic acid is a hydrophobic molecule, necessitating the use of dimethyl sulfoxide (DMSO) or alcohol as a solvent in the study. A 0.5% DMSO solution is believed to have no impact on the OHCs.[16,17]

Distortion Product Otoacoustic Emissions (DPOAEs) are acoustic energy measured from the ear canal, produced by the nonlinear interaction of 2 pure tones in the cochlea.[18] They are typically generated under healthy conditions but may be reduced or absent in pathological cochlear regions.[19]

Antioxidant treatments addressing oxidative imbalance in NIHL show promise, but more research is needed on their long-term effects. Their clinical application is limited by low bioavailability, making it hard to achieve effective levels in vivo. Therefore, regulating retinoid concentrations remains crucial for inner ear development and maintenance.

In this study, the electrophysiological effects of intratympanic RA application on post-acoustic trauma were aimed to be investigated.

## METHODS

### Experimental Design

This study was approved by the ethical committee for Experimental Research on Animals of Başkent University, Türkiye (18/11-2013-DA/13/48; 13-52).

In the power analysis conducted prior to the study, it was determined that conducting the study with 7 rats in each group would be appropriate. Twenty-one healthy Sprague–Dawley male rats were included in the study and were divided into 3 groups (7 rats per group); the first group was referred to as the experimental group and received RA injections, the second group was the alcohol group (the RA solution (1%) used in the study was prepared in alcohol (96%)), and the last was the control group.

No treatment was administered to the rats in the control group after noise exposure; they did not receive RA, alcohol, or a placebo injection. To evaluate the effect of RA application on signal-to-noise ratio (SNR) levels following noise exposure, the control group remained untreated, resulting in no observed changes in their SNR levels.

During the study, 1 rat from each group died because of acute otitis media.

Blood samples were taken from each group before sound exposure and after injections. All biochemical parameters of the rats were similar between the groups. Blood samples were collected to assess

inflammatory cytokines, stress hormones, blood glucose, lipid profiles, and liver and kidney enzymes, enabling the evaluation of physiological parameters and the detection of any underlying conditions affecting study outcomes.

The first group received intratympanic RA treatment in 2 doses: 1 hour after acoustic trauma and on the second day after trauma. Each application involved approximately 0.1 cc (enough to fill the middle ear) of a RA solution (1 mg per cc) administered through a dental injector under otoscopic guidance into the posteroinferior quadrant of the tympanic membrane.

To evaluate the effects of the alcohol (as the RA solvent) after acoustic trauma, 0.1 mL of alcohol was injected into the second group of rats concurrently with RA application in the first group. The third group did not receive any treatments after acoustic trauma.

**Measurement of Otoacoustic Emissions and Distortion Product Otoacoustic Emissions**

Otoacoustic emission measurements of all rats were done during a pre-acoustic trauma period. Twenty-one male rats with normal hearing were exposed to a noise level of 110 dB SPL within a double-walled, double-chamber silent cabin with 60 dB noise isolation for 12 hours. The DPOAE measurements of all rats were done after the acoustic trauma.

One hour after acoustic trauma, RA injections were performed on the first group. The DPOAE measurements were done again 48 hours after the second RA dose. The DPOAE measurements of the alcohol and control groups were done concurrently.

Rats had free access to food and water, with a background noise level under 50 dB at 25°C on a 12-hour light-dark cycle.

Otoscopic examinations of all rats were done under general anesthesia; debris and plugs in the external ear canal were cleaned. Rats with intact tympanic membranes were included in the study.

Distortion product otoacoustic emissions (2f1-f2 cubic distortion product components) were measured using an ILOv6 (Otodynamics Ltd, Hatfield, United Kingdom) in general diagnostic mode. The ratio between f2 and f1 frequencies (f2/f1) was adjusted to 1.2. The volume of the stimulus for the f1 frequency was designated L1, and L2 was used for the f2 frequency. L1 and L2 were set at a level of 10 dB SPL (L1 = 6, L2 = 55). The results were shown as geometric averages of primary tones (f1, f2). Otoacoustic emissions were stimulated using 2 different speakers for the 2 stimuli (f1 and f2) in the outer ear canal. The DPOAEs were measured at f1 and f2 frequencies with a microphone in the outer ear canal. The DPOAEs can be reliably recorded between 500 and 8000 Hz and provide frequency-specific measurements. The performance is weakest at 500 and 1000 Hz, best at 4000 Hz, and moderate at 2000 and 8000 Hz. The test period was approximately 30 seconds. The DPOAE amplitudes above the noise threshold (over 3 dB) were considered meaningful. Measurements were performed in a room where noise levels did not exceed 50 dB.

Electrophysiological measurements and intratympanic injections were carried out under general anesthesia with intramuscular administrations of 40 mg/kg of ketamine hydrochloride (HCl) (Ketalar, Pfizer, Istanbul, Türkiye) and 5 mg/kg of xylazine HCl (Rompun, Bayer, Istanbul, Türkiye).

**Statistical Analysis**

As 3 rats died during the study, statistical analysis was performed on the results from a total of 18 rats (6 rats in each group).

IBM SPSS Statistics Version 18.0 software for Windows (SPSS Inc.; Chicago, IL, USA) was used for statistical analysis. The DPOAE levels for each frequency were analyzed using a Kruskal–Wallis test to compare multiple groups, and a Mann–Whitney *U* test was used for the comparison of the results from the first and second doses of RA. $P < .05$ was considered to be statistically significant.

## RESULTS

Otoscopic examinations and DPOAE measurements were performed on all rats in the pre-trauma period. Rats were exposed to noise at 110 dB SPL (sound pressure level) for 12 hours in a free place and DPOAE was repeated. Signal-to-noise ratio values of the DPOAE measurements were separately assessed at 1 kHz, 1.4 kHz, 2 kHz, 2.8 kHz, 4 kHz, 6 kHz, and 8 kHz frequencies before and after the trauma in each group.

Each of the 3 groups was found to be similar ($P > .05$) at the OAE assessment during the pre-acoustic trauma phase when DPOAE SNR levels for each group were analyzed at frequencies of 1 kHz, 1.4 kHz, 2 kHz, 2.8 kHz, 4 kHz, 6 kHz, and 8 kHz.

Laboratory findings were similar in each group, and no statistical difference was found in any group.

For the first group, DPOAE measurements were performed following the noise exposure (as in all the groups), and RA was administered 1 hour afterward. The DPOAE measurements were performed after the first dose. Then, 48 hours later, a second dose of RA was injected, and DPOAE measurements were performed again 48 hours after the second administration of RA. After the administration of the first dose of RA and especially after the second dose, a statistically significant difference was detected between the groups. Significant differences were found in the RA-injected group after the first and second doses at frequencies of 1.4, 2, 2.8, 6, and 8 kHz. A statistically significant difference was observed between the groups ($P < .001$).

In the first group (RA group), a significant difference was detected at 1.4, 2, 2.8, 6, and 8 kHz after the first dose and the second dose ($P < .05$).

No significant differences were found between the alcohol and control groups in terms of SNR values ($P > .05$).

Table 1 shows the SNR values after the first and second RA treatment with *P*-values on the first group.

Figure 1 shows SNR values in each frequency in all groups after acoustic trauma.

Figure 2 shows SNR in each frequency in all groups after the second dose of treatment.

**Table 1.** Comparison of SNR Values After the First and Second Retinoic Acid Injections Using the Mann–Whitney *U* test

| SNR | *P* |
|---|---|
| 1 kHz | .748 |
| 1.4 kHz | .003 |
| 2 kHz | .013 |
| 2.8 kHz | .019 |
| 4 kHz | .056 |
| 6 kHz | .034 |
| 8 kHz | .007 |

## DISCUSSION

One of the major causes of sensorineural hearing loss is exposure to loud noise, especially in industrial communities, which causes loss or dysfunction of the motility of the OHCs.

Stereocilia loss in hair cells may result in many structural changes, such as collapse of the organ of Corti, loss of spiral ganglion cells, loss of spiral ligament fibrocytes, or atrophy of the stria vascularis.[20]Death of hair cells is caused by the effects of hypoxia and free radicals, resulting in a decrease in cochlear blood flow.[21]

Hypoxia produces free radicals, which contribute to hair cell death.[18]

Formation of free oxygen species and nitrate radicals (ROS/RNS) in the cochlea can continue up to 7-10 days after exposure.[21,22]

Under physiological conditions, ROS increase is balanced by an effective endogenous antioxidant system, maintaining redox balance. However, in non-physiological conditions such as acoustic trauma, ROS concentrations can increase significantly and abruptly, potentially overwhelming the cochlea's endogenous antioxidant system. As a result, cellular damage cannot be repaired, leading to the death of IHCs and especially OHCs, which in turn triggers the reactivation of necrosis or apoptosis pathways.[4] An increase in the rates of karyorrhexis and karyopyknosis, which are indicators of apoptosis in hair cells following experimentally induced acoustic trauma, is evidence supporting apoptosis.[23] In response to oxidative stress, lipid peroxidation and necrosis in the organ of Corti occur rapidly, while apoptosis, which is driven by oxidative stress-induced DNA and protein damage, develops more slowly and typically manifests several days after noise exposure.[24]

Accordingly, during this period, intervention with antioxidant agents may enable recovery in NIHL.[4]

Studies support that antioxidant agents such as vitamins A, C, and E, magnesium, glutathione, L-acetylcysteine, D-methionine, and alpha-tocopherol can provide otoprotective effects by counteracting cochlear oxidative stress and preventing threshold shifts induced by noise exposure.[25,26]

In the study, based on this information, the effects of intratympanic RA administration following experimentally induced acoustic trauma were aimed to be demonstrated using DPOAE measurements, which reflect OHC function.

Otoacoustic emissions are produced by the OHCs. When the OHCs are damaged due to hypoxia, ototoxic drugs, or acoustic trauma, the production of OAEs is inhibited. The DPOAE is a test that measures OHC function and is also an objective method used to assess the hearing and cochlear function of research animals.[27] For this reason, DPOAE has been frequently used to test the effects of noise on OHCs.[27]

It was demonstrated that after acoustic trauma, DPOAE measurements were consistent with sensorineural hearing loss, and that condition is a finding consistent with OHC damage.

Studies in rats suggest that RA can stimulate hair cell regeneration in the organ of Corti affected by ototoxicity in artificial tissue cultures, and that its early use has the potential to reduce hair cell loss and threshold shifts induced by noise.[15]

When the generation of ROS exceeds the capacity of the antioxidant system to neutralize them, it can result in morphological nuclear alterations, DNA damage, lipid peroxidation, and eventually lead to necrosis or apoptosis.

As a result, the use of antioxidants that can scavenge ROS and nitrogen radicals within 3 days after noise exposure can decrease hearing loss.[22]

Retinoic acid is an active derivative of vitamin A and plays a significant role in the embryonic development of the inner ear, homeostasis, cell morphogenesis, as well as mature tissue differentiation.[28]

Retinoic acid plays an important role in the development of the organ of Corti and has an impact on the differentiation of presensory cells into hair and support cells. Retinoic acid can also create pre-cochlear cell populations that appear like pre-neural cells.[29,30]

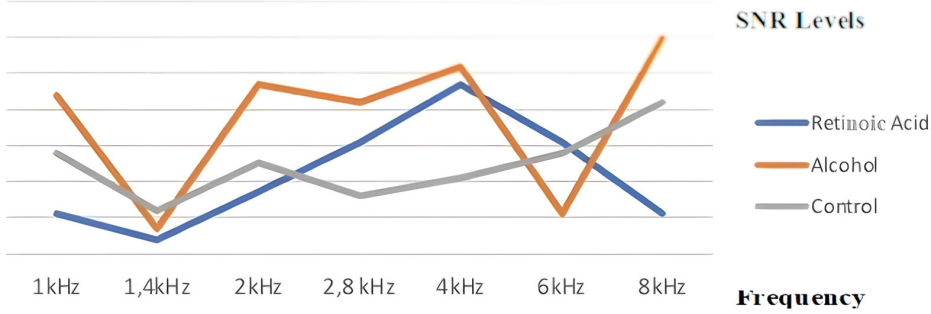


**Figure 1.** Signal-to-noise ratio (SNR) in 1, 1.4, 2, 2.8, 4, 6, 8 kHz between groups after acoustic trauma.

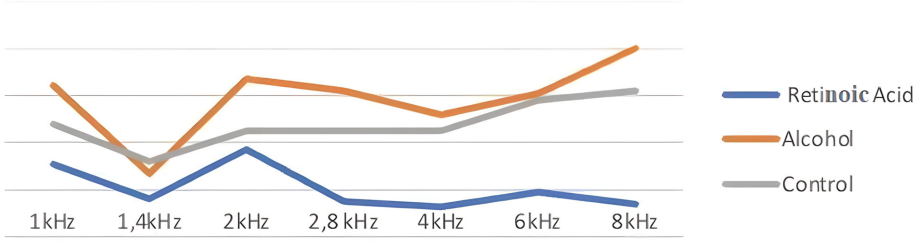


**Figure 2.** Signal-to-noise ratio (SNR) between groups after the second dose of intratympanic retinoic acid treatment. Significant increase in 1, 1.4, 2, 2.8, 4, 6, and 8 kHz in SNR after the retinoic acid injection is remarkable.

Also decrease in vitamin A levels is related to the increased sensitivity of the inner ear to noise.[31]

Shim et al (2009),[21] treated mice with RA after exposure to noise can decrease hair cell loss and diminish hearing threshold. In addition, Ahn et al (2005)[32] found that hearing thresholds in mice fed All Trans Retinoic Acid (ATRA) infused sesame oil on 3 successive days before/after noise exposure were better than in the control group.

A recent study also showed hearing loss with decreased amplitude of wave I in auditory brainstem response after NIHL. Although it was found that the hearing threshold in ABR was completely recovered after noise exposure, ATRA and selective RA receptor agonists also showed a significant decrease in wave I.[33]

In this study, RA was injected intratympanically not only to decrease systemic side effects but also to obtain greater impact by increasing the effective concentration of RA in the inner ear. Alcohol was used as the solvent since RA is a hydrophobic molecule. Gross et al (2010)[34] used 0.5% DMSO as the RA solvent and demonstrated that this dose had a negative effect on the OHCs and on gene expression.

To evaluate the effects of alcohol, diluted alcohol (96%) at 1% was used, and no significant difference was found.

Despite numerous studies on NIHL, a clear and accepted therapeutic approach has not yet been established. Although there are no approved drugs for this patient group, the effectiveness of agents highlighted in clinical trials remains controversial. The use of antioxidants in experimental models is also limited, and the results are inconsistent.[35]

The way antioxidants are metabolized and utilized in the body is influenced by genetic variations, leading to different responses to antioxidant therapies in individuals, which can also reduce the bioavailability of antioxidants.

In conclusion, the experimental animal study found that intratympanic RA injection applied after acoustic trauma had a protective effect against acoustic trauma. However, these results should be supported by further studies in humans. Furthermore, it is believed that investigating the use of RA prior to exposure to loud noise, along with its potential safeguarding effects on auditory health, will significantly enrich the existing body of literature.

## CONCLUSION

Use of RA after noise exposure can protect hearing when noise levels reach a degree that can harm the inner ear and auditory system or when acoustic trauma occurs. Retinoic acid is an agent that has been clinically tested and can be safely used orally in humans. It is believed that intratympanic RA injection during the early post-trauma period has a protective effect against acoustic trauma in rats. However, further studies are needed to determine the safest and most effective dosage and treatment time for clinical use.

For this reason, while current pharmacotherapy research is primarily focused on antioxidants, a more effective approach may involve targeting multiple therapeutic pathways beyond just oxidative stress.

**Data Availability Statement:** The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

**Ethics Committee Approval:** This study was approved by the ethical committee for Experimental Research on Animals of Başkent University, Türkiye (approval number:DA/13/48;13-52; date: November 18, 2013).

**Informed Consent:** Since this is an animal study, informed consent was not applicable.

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**Declaration of Interests:** The authors have no conflicts of interest to declare.

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