RESEARCH ARTICLE

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Investigating the Role of Stochastic Resonance in Tinnitus Development among Patients with Axonal Polyneuropathy

Dominika Hojná[1],
Pavel Kunc[1,2],
Oldřich Vyšata[*1,2]

ABSTRACT

Tinnitus is a prevalent auditory disorder characterized by the perception of sound without an external source, often significantly impacting quality of life. The Stochastic Resonance (SR) hypothesis suggests that tinnitus arises as a compensatory mechanism where the auditory system amplifies internal neural noise to enhance signal detection in response to hearing loss. This study explores the potential link between axonal loss in peripheral nerves and the development of tinnitus through SR in patients with axonal polyneuropathy. We recruited 82 patients exhibiting clinical symptoms of distal symmetric sensory or sensorimotor polyneuropathy. Electrophysiological assessments, including nerve conduction studies and electromyography, were performed, and the occurrence of tinnitus was evaluated using the Tinnitus Severity Index and Visual Analog Scale. Logistic regression analysis revealed that decreased amplitudes of the Compound Motor Action Potential (CMAP) of the tibial and peroneal nerves are significantly associated with a higher likelihood of experiencing tinnitus ($p = 0.012$ and $p = 0.043$, respectively). Additionally, increased Motor Conduction Velocity (MCV) of the peroneal nerve was linked to the presence of tinnitus ($p = 0.028$). These findings support the hypothesis that axonal loss in peripheral nerves correlates with axonal loss in the auditory nerve, potentially leading to tinnitus through the mechanism of stochastic resonance. Modulation of ion channel function may be a compensatory response to axonal loss, contributing to increased neural noise and the perception of tinnitus. Our study enhances the understanding of the pathophysiology of tinnitus in patients with axonal polyneuropathy and suggests potential targets for future therapeutic interventions. Further research is necessary to validate these conclusions and to investigate the mechanisms by which ion channel modulation affects both peripheral and central nervous systems.

Keywords: Tinnitus, Axonal Polyneuropathy, Stochastic Resonance, Compound Motor Action Potential, Motor Conduction Velocity, Ion Channel Modulation, Auditory Nerve, Electrophysiology, Neural Noise, Peripheral Nerve Degeneration.

[1]Department of Neurology, Faculty of Medicine in Hradec Králové, Charles University, Šimkova 870, Hradec Králové, 500 03 Czech Republic
[2]Department of Neurology, University Hospital Hradec Králové, Sokolská 581, 500 05 Hradec Králové – Nový Hradec Králové, Czech Republic

***Send correspondence to**
Oldřich Vyšata
Department of Neurology, Faculty of Medicine in Hradec Králové, Charles University, Šimkova 870, Hradec Králové, 500 03 Czech Republic, Tel: 420 725923797, Email: mailto:oldrich.vysata@fnhk.cz

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INTRODUCTION

Tinnitus is a common auditory disorder characterized by the perception of phantom sounds such as ringing, buzzing, or hissing in the absence of an external source. It can significantly impair quality of life by affecting sleep, concentration, and emotional well-being. Although electrophysiological techniques, including auditory evoked potentials and electrocochleography, can assess auditory pathway function, they cannot definitively confirm the presence of tinnitus[1].

Recent evidence suggests that Stochastic Resonance (SR), a principle originally described in physics, may play a key role in tinnitus development. According to this model, the auditory system compensates for hearing loss by amplifying internal neural noise, thereby improving the detection of weak sound signals[2]. While this mechanism can enhance auditory sensitivity, it may also produce tinnitus as an unintended consequence. Understanding SR could thus advance our grasp of tinnitus pathophysiology and guide the development of more effective treatments[3]. In cases of acute or chronic hearing impairment, SR-based compensation helps maintain auditory sensitivity, but may also lead to phantom percepts[4-6].

Another proposed mechanism for tinnitus involves maladaptive plasticity in the central nervous system. This process can cause abnormal neuronal activity in both auditory and non-auditory brain regions, increasing spontaneous firing rates and neural synchrony associated with phantom sound perception[7]. Such central maladaptive changes may also lead to hyperacusis[8]. Neuroimaging studies have identified structural and functional alterations in auditory and limbic brain areas, as well as abnormal resting-state activity patterns in regions such as the bilateral insula, middle temporal gyrus, inferior frontal gyrus, parahippocampal gyrus, posterior cerebellar lobe, and right superior frontal gyrus, with decreased activity in the left cuneus and right thalamus[9,10].

While SR has been largely investigated in the context of auditory processing, its relevance may extend to conditions involving peripheral nerves. Axonal polyneuropathy, characterized by peripheral nerve fiber degeneration, leads to symptoms such as numbness, weakness, and pain[11]. Chronic Idiopathic Axonal Polyneuropathy (CIAP) primarily affects peripheral nerves and raises questions about potential interactions with the auditory system[12,13]. Given that the auditory nerve is also a peripheral nerve, it is plausible that axonal loss in polyneuropathy could reduce auditory input, prompting compensatory SR-driven increases in internal neural noise. These changes, intended to restore normal hearing sensitivity, may be misinterpreted as tinnitus[14].

Building on this concept, we hypothesize that axonal damage in the auditory nerve, akin to that observed in axonal polyneuropathy, may contribute to tinnitus through SR-mediated compensation. To explore this potential connection, we examined patients with clinical manifestations of axonal polyneuropathy using nerve conduction studies and needle Electromyography (EMG). We then evaluated the incidence of tinnitus in these patients, seeking to determine whether the extent of axonal damage correlates with tinnitus occurrence and to gain deeper insight into the underlying mechanisms of tinnitus generation in the context of axonal polyneuropathy.

METHODS

Participants

Patients exhibiting clinical symptoms of distal symmetric sensory or sensorimotor polyneuropathy were recruited from referrals to the electromyography (EMG) laboratory. The most common clinical manifestations included numbness, tingling, burning sensations, and muscle weakness predominantly in the lower extremities.

Selection Criteria

We selected patients who met the EMG criteria for axonal polyneuropathy and those with normal EMG findings. The EMG criteria for axonal polyneuropathy were defined as follows:

- **Reduced Amplitude of Compound Motor Action Potential (CMAP)**: Indicative of axonal loss in motor nerves.
- **Reduced Amplitude of Sensory Nerve Action Potential (SNAP)**: Suggesting axonal degeneration in sensory fibers.
- **Relatively Preserved Conduction Velocities and Distal Latencies**: Differentiating axonal polyneuropathy from demyelinating neuropathies.

Patients with demyelinating features or other neuromuscular disorders were excluded from the study.

Assessment of Tinnitus

Within this cohort, the presence of tinnitus was assessed using the Tinnitus Severity Index (TSI) and the Visual Analog Scale (VAS). These validated tools quantified the intensity and impact of tinnitus on the patients' quality of life.

Electrophysiological Measurements

The following EMG parameters were measured:

- **Distal Motor Latency (DML):** Time from nerve stimulation to muscle response onset, measured in milliseconds.
- **Amplitude of Compound Motor Action Potential (CMAP):** Peak voltage of the motor response, reflecting the number of functioning motor axons.
- **Motor Conduction Velocity (MCV):** Speed of impulse transmission in motor nerves (nervus peroneus and tibialis), measured in meters per second.
- **Sensory Conduction Velocity (SCV):** Speed of sensory impulse transmission, measured in meters per second.

Table 1: Logistic Regression Results for Predicting Tinnitus Occurrence Based on Electrophysiological Parameters.

Variable	Coefficient	Standard Error	z-value	p-value	95% Confidence Interval
CMAP n. tibialis	-0.1908	0.076	-2.515	0.012	[-0.340; -0.042]
MCV n. peroneus	0.0701	0.032	2.194	0.028	[0.007; 0.133]
CMAP n. peroneus	-0.4904	0.242	-2.026	0.043	[-0.965; -0.016]

Note: This table presents the coefficients (coef), standard errors (std err), z-values (z), p-values (P>|z|), and 95% confidence intervals ([0.025; 0.975]) for each predictor variable.

- **Amplitude of Sensory Nerve Action Potential (SNAP):** Peak voltage of the sensory response, indicating the number of functioning sensory axons.

For each parameter, the average values from both lower extremities were calculated and used for statistical analysis.

Statistical Analysis

The predictive value of the electrophysiological parameters for the occurrence of tinnitus was evaluated using logistic regression analysis. A logistic regression with backward selection was performed:

1. **Initial Model**: Started with a full model including all predictors (DML, CMAP amplitude, MCV, SCV, SNAP amplitude).
2. **Backward Selection**: Sequentially removed predictors with the highest p-values.
3. **Final Model**: Continued the process until all remaining predictors were statistically significant at the $\alpha = 0.05$ level.

Demographic characteristics (age, gender, duration of symptoms) between the groups with and without tinnitus were compared using Student's t-test after confirming normal distribution with the Shapiro-Wilk test. For the comparison of categorical variables, Fisher's exact test was used.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board. Informed consent was obtained from all participants prior to inclusion in the study.

RESULTS

Demographic Data

- **Age:** The mean age of subjects with tinnitus was 64.39 years (SD = 16.82), while subjects without tinnitus had a mean age of 64.95 years (SD = 12.37). A Student's t-test revealed no statistically significant difference in mean age between the two groups (t = -0.1735; p = 0.8627).
- **Gender:** Fisher's Exact Test indicated no statistically significant difference in gender distribution between subjects with and without tinnitus (odds ratio = 0.746; p = 0.435).

Subject Distribution

- Total Subjects: 82
  - Males with Tinnitus: 15
  - Males without Tinnitus: 23
  - Females with Tinnitus: 14
  - Females without Tinnitus: 30

Logistic Regression Analysis

To assess the predictive value of electrophysiological parameters for the occurrence of tinnitus in patients with axonal polyneuropathy, a logistic regression analysis with backward selection was conducted. The final model identified three significant predictors:

1. **Decreased CMAP Amplitude of the Tibial Nerve:** A negative coefficient (coef = -0.1908; p = 0.012) indicates that lower amplitudes of the Compound Motor Action Potential (CMAP) of the tibial nerve are associated with a higher likelihood of experiencing tinnitus.
2. **Increased MCV of the Peroneal Nerve:** A positive coefficient (coef = 0.0701; p = 0.028) suggests that higher Motor Conduction Velocity (MCV) of the peroneal nerve is linked to an increased risk of tinnitus.
3. **Decreased CMAP Amplitude of the Peroneal Nerve:** A negative coefficient (coef = -0.4904; p = 0.043) shows that reduced CMAP amplitudes of the peroneal nerve are significantly associated with the occurrence of tinnitus (**Table 1**).

Description of Predictor Variables:

- **CMAP n. tibialis:** Amplitude of the Compound Motor Action Potential of the tibial nerve, reflecting motor axonal integrity.
- **MCV n. peroneus:** Motor Conduction Velocity of the peroneal nerve, indicating the speed of nerve impulse transmission.
- **CMAP n. peroneus:** Amplitude of the Compound Motor Action Potential of the peroneal nerve, reflecting motor axonal integrity.

These parameters were evaluated to determine their predictive value for the occurrence of tinnitus in patients with axonal polyneuropathy.

DISCUSSION

This study investigated the association between axonal degeneration in patients with axonal polyneuropathy

and the occurrence of tinnitus. Our findings demonstrate that reduced Compound Motor Action Potential (CMAP) amplitudes in both the tibial and peroneal nerves are significantly associated with an increased likelihood of experiencing tinnitus. In addition, we observed that elevated Motor Conduction Velocity (MCV) of the peroneal nerve correlates with the presence of tinnitus.

These results lend support to the hypothesis that axonal loss in peripheral nerves may parallel similar pathology in the auditory nerve, potentially initiating tinnitus through stochastic resonance mechanisms. The reduction in CMAP amplitudes is indicative of axonal damage, which could enhance neural noise and lead to the perception of tinnitus.

The observed increase in peroneal nerve MCV among patients with tinnitus is particularly noteworthy. Axonal damage typically reduces conduction velocity; thus, the enhanced MCV suggests an adaptive or compensatory modulation of ion channel function. Such modulation may induce hyperexcitability in the remaining fibers, increasing conduction speed and potentially exacerbating tinnitus symptoms. Previous research employing non-invasive "threshold tracking" techniques has shown that patients with polyneuropathy have elevated persistent sodium currents, contributing to axonal hyperexcitability[15].

Ion channel modulation likely influences both peripheral nerve conduction properties and auditory nerve transmission. Increased ion channel activity not only augments neural noise but may also facilitate pathological auditory processing, ultimately contributing to tinnitus generation. Consequently, our data suggest that axonal loss alone is insufficient to explain tinnitus onset and that compensatory mechanisms particularly ion channel modulation play a significant role.

Several limitations should be considered. The relatively small sample size and the absence of direct auditory nerve assessments limit the strength of our conclusions. Future studies should incorporate comprehensive audiological evaluations and consider functional imaging of the central nervous system to clarify the precise interplay between peripheral nerve damage and central auditory processing[16].

CONCLUSION

Our findings identify a significant relationship between decreased CMAP amplitudes of the tibial and peroneal nerves and the occurrence of tinnitus in patients with axonal polyneuropathy. We also demonstrate that increased peroneal nerve MCV is associated with tinnitus. These results suggest that the organism may respond to axonal degeneration through ion channel modulation, thereby enhancing auditory nerve transmission and contributing to tinnitus generation. Moreover, ion channel modulation may help explain the unexpected increase in motor conduction velocity observed in patients with polyneuropathy and tinnitus.

This study advances our understanding of tinnitus pathophysiology in the context of axonal polyneuropathy, underscoring potential targets for future interventions. However, further research is needed to confirm these findings and elucidate the mechanisms by which ion channel modulation influences both peripheral and central nervous system processes involved in tinnitus perception. Although the direct link between axonal polyneuropathy and tinnitus development via stochastic resonance remains to be fully established, the SR model provides a plausible conceptual framework. Additional studies are required to explore this potential relationship and to better understand how peripheral nerve damage in axonal polyneuropathy may interact with central auditory processing mechanisms.

CONFLICTS OF INTEREST AND SOURCE OF FUNDING

The authors declare no conflict of interest.

REFERENCE

1. Fan S, Li S. Objective detection of tinnitus based on electrophysiology. Brain Sci. 2022;12(8):1086.
2. Forster D, Sheikh AS, Lücke J. Neural simpletrons: Learning in the limit of few labels with directed generative networks. Neural Comput. 2018;30(8):2113-74.
3. Prendergast G, Tu W, Guest H, Millman RE, Kluk K, Couth S, et al. Supra-threshold auditory brainstem response amplitudes in humans: Test-retest reliability, electrode montage and noise exposure. Hear Res. 2018;364:38-47.
4. Krauss P, Tziridis K, Metzner C, Schilling A, Hoppe U, Schulze H. Stochastic resonance controlled upregulation of internal noise after hearing loss as a putative cause of tinnitus-related neuronal hyperactivity. Front Neurosci. 2016;10:597.
5. Schilling A, Tziridis K, Schulze H, Krauss P. The stochastic resonance model of auditory perception: A unified explanation of tinnitus development, Zwicker tone illusion, and residual inhibition. Prog Brain Res. 2021;262:139-57.
6. Krauss P, Tziridis K. Simulated transient hearing loss improves auditory sensitivity. Sci Rep. 2021;11(1):14791.
7. Sedley W. Mechanisms of tinnitus: Neural correlates and treatment implications. Nat Rev Neurol. 2019;15(4):213-24.
8. Zeng FG. Tinnitus and hyperacusis: Mechanisms and therapies. Curr Opin Neurobiol. 2013;23(3):361-66.
9. Adcock K, De Ridder D, Vanneste S. Structural and Functional MRI-Based Neuroimaging in Tinnitus. Springer Sci Rev. 2024.
10. Chen YC, Wang F, Wang J, Bo F, Xia W, Gu JP, et al. Resting-state brain abnormalities in chronic subjective tinnitus: a meta-analysis. Front Hum Neurosci. 2017;11:22.
11. Mirian A, Aljohani Z, Grushka D, Florendo-Cumbermack A. Diagnosis and management of patients with polyneuropathy. CMAJ. 2023;195(6):E227-33.
12. Notermans NC, Wokke JH, Van der Graaf Y, Franssen H, Van Dijk GW, Jennekens FG. Chronic idiopathic axonal polyneuropathy: a five year follow up. J Neurol Neurosurg Psychiatry. 1994;57(12):1525-7.

13. Zis P, Sarrigiannis PG, Rao DG, Hewamadduma C, Hadjivassiliou M. Chronic idiopathic axonal polyneuropathy: a systematic review. J Neurol. 2016;263:1903-10.

14. Schilling A, Sedley W, Gerum R, Metzner C, Tziridis K, Maier A, et al. Predictive coding and stochastic resonance as fundamental principles of auditory phantom perception. Brain. 2023;146(12):4809-25.

15. Kuwabara S, Misawa S. Pharmacologic intervention in axonal excitability: in vivo assessment of nodal persistent sodium currents in human neuropathies. Curr Mol Pharmacol. 2008;1(1):61-7.

16. Hu J, Cui J, Xu JJ, Yin X, Wu Y, Qi J. The neural mechanisms of tinnitus: a perspective from functional magnetic resonance imaging. Front Neurosci. 2021;15:621145.