ORIGINAL ARTICLE

I’ Wave Auditory Brainstem Response as a Possible Indicator of Noise-Induced Cochlear Synaptopathy

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ABSTRACT

Objectives: Cochlear synaptopathy, caused by the destruction of synaptic connections due to aging, noise exposure, and ototoxic agents, is defined as auditory dysfunction despite the normal hearing threshold, specifically in challenging situations. One of the main obstacles in synaptopathy studies and the integration and generalization of research findings is the need for a valid diagnostic test. Although the issue of identifying synaptopathy has received considerable critical attention, little agreement is available on a valid and efficient diagnostic method for cochlear synaptopathy.

Material & Methods: A critical review was conducted on previous animal and human studies addressing cochlear synaptopathy, with particular emphasis on the paired-click paradigm and I’ wave electrophysiological assessments. Subsequently, pertinent physiological and biophysical models elucidating excitatory postsynaptic potentials at the inner hair cell ribbon synapse were analyzed. Finally, the feasibility and limitations of I’ wave recording were theoretically evaluated, with recommendations for future validation studies.

Results: A review of the existing evidence and analysis of biophysical modeling data indicate that the I’ wave in the auditory brainstem response, particularly when using the paired-click paradigm, represents the excitatory postsynaptic potential (EPSP) generated at the inner hair cell ribbon synapse.

Conclusion: The present hypothesis attempts to bring forward a non-invasive tool that can investigate synaptic function. It sheds new light on future studies in cochlear synaptopathy by suggesting the I’ wave as its biomarker.

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Introduction

The present hypothesis is based on the capability of the I’ wave to represent the function of the Inner Hair Cell (IHC) ribbon synapse. This suggests the potential for assessing synaptic function in humans through a non-invasive method. This approach could serve as an effective clinical tool for identifying cochlear synaptopathy.

Cochlear Inner Hair Cell Synapse

The auditory system is anatomically and physiologically optimized for precise and rapid coding, depending on faithful synaptic transmission at Synapses between IHCs and cochlear nerve fibers (1). These synapses establish the exclusive pathway for transmitting auditory information to the central auditory system, conveying the signal’s frequency,

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intensity, and temporal characteristics across an immense range (2). Accurate and faithful transmission of temporal cues is critical for the neural representation of sound source localization, pitch perception (3), and spectral characteristics of complex sounds such as speech (2).

Despite typical synapses driven by an action potential, afferent IHC synapses are driven by graded membrane potential variation in response to hair bundle displacement following sound exposure and mechano-electrical transduction. This sensory transduction mechanism, where the synapse responds to graded receptor potentials rather than action potentials, is characteristic of all sensory cell types in which a presynaptic electron-dense structure called a ribbon (4) tethers synaptic vesicles, anchored in their active zone (5). This particular type of synapse provides the hair cell's astonishing temporal precision in encoding the acoustic stimulus's fine temporal structure (4). Regardless of size or location, the synaptic ribbon creates a single, concave postsynaptic density (PSD), increasing the overall area of the presynaptic active zone. The larger PSDs contribute to the special properties of this synapse (6). Almost all IHC synapses are glutamatergic, releasing glutamate at a consistently high and sustained rate. This glutamate release generates a firing pattern in primary auditory neurons by binding to AMPA receptors at the afferent terminal. The presence of AMPA receptors in the PSD of the central nervous system is considered to represent the speed of synaptic transmission (7). At the IHC synapse, a large pool of extra-synaptic glutamate receptors facilitates rapid changes in the quantity and type of synaptic receptors, potentially ensuring a dynamic postsynaptic response. Accordingly, the mediation of AMPA receptors in producing the excitatory postsynaptic potentials (EPSP) of spiral ganglion afferent fibers has been suggested (1). In the study of single-unit recording from afferent nerve endings in frogs, substantial EPSPs and their participation in precise temporal coding have been proposed (6). On the other hand, a consensus exists regarding the heightened vulnerability of this type of synapse to external stress (8), which disrupts temporal coding capabilities (9). This has prompted a particular focus on the role of ribbons in cochlear synaptopathy.

Cochlear synaptopathy

The decline in the number of synapses or cochlear nerve terminals (8) caused by the destruction of synaptic connections due to aging (9-11), noise exposure (12-14), and ototoxic agents (15) is known under the general term cochlear synaptopathy. Cochlear synaptopathy causes significant neurodegeneration without concurrent damage to IHCs (12). Nonetheless, given that IHC fibers comprise 95% of the cochlear neuronal population, it appears reasonable to anticipate that their dysfunction may result in significant auditory consequences, even with normal hearing thresholds The involvement of the neuronal population with varying spontaneous firing rates in the coding of stimuli at both threshold and supra-threshold levels (16), along with studies demonstrating the higher vulnerability of low spontaneous rate (LSR) attributed to disparities in mitochondrial quantity, glutamate uptake mechanisms, and calcium channels (17), has substantiated this assertion. Therefore, limited deafferentation reduces the capacity to encode stimuli in complex situations without impacting tone detection in quiet environments (12). One of the main obstacles in synaptopathy studies and the integration and generalization of research findings is the need for a valid diagnostic test (18-22). Consequently, the main challenge many researchers face in this domain is developing and validating specific tests (20). Recent efforts to explore the function of the inner hair cell (IHC) synapse have led to the development of innovative methods. These include simultaneous recording of calcium ion (Ca^{2+}) flow in the hair cell (presynaptic) and the response of the afferent terminal (postsynaptic). Researchers are also employing genetic investigations, using mutated mice to study defects in synaptic proteins (4). Additionally, monitoring exocytic fusion and recovery into the vesicle membrane is achieved through changes in membrane capacitance using the patch-clamp technique (1). High-resolution imaging (4), elective immunostaining, and confocal microscopy (12) are among the most common methods used to diagnose synaptic loss in animal models directly. However, applying such invasive methods is infeasible in humans, at least before death (18). Therefore, numerous efforts have been undertaken to develop an indirect method with appropriate sensitivity, specificity, and efficiency to identify cochlear synaptopathy (20-23). For this purpose, the auditory brainstem response (ABR) (9, 12, 24-32), Otoacoustic emission (OAE) (9, 25, 26, 30), the envelope following response (EFR) (33), Electrocochleography (29, 34), ABR in noise (24), high-frequency audiometry (35), middle ear muscles acoustic reflex (36, 37), and paired-click paradigm (38, 39) were introduced. However, a reliable and effective diagnostic approach for cochlear synaptopathy is still not agreed upon. (7, 20, 21, 29, 35, 37, 38). Furthermore, a comprehensive investigation examining the functionality of ribbon synapses in living individuals has yet to be conducted (40). The

present hypothesis aims to put forward a non-invasive technique capable of examining synapse function, a pivotal role in addressing unresolved questions. It also sheds new light on future studies in cochlear synapse function by introducing I' wave as its tool.

The I' wave

The I' wave was introduced (41) in auditory evoked potentials at a latency of less than 1 millisecond at high intensities in normal subjects. The study (42) aimed to ascertain the anatomical origin of the wave, indicating that the I' wave may potentially represent the excitatory postsynaptic potentials (EPSP) following the activity of the afferent dendrites of the VIIIth cranial nerve. Moore had previously reported the possibility of recording the evoked EPSPs without CAP, using the paired-click paradigm (41). This stimulation paradigm has been the subject of recent investigations in animal models (38, 39) and human studies (43-45) to elucidate synaptic function through the computation of EPSPs. In explaining the recording of the I' wave as an EPSP, the presentation of the initial click triggers the generation of APs along the cochlear nerve, and produces from I' to V waves in response. The presentation of the second click during the refractory period reduces or eliminates the possibility of AP generation. Thus, from a theoretical point of view, the response evoked by the second click reflects the summation of the EPSP activity in the postsynaptic membrane (42), originating from the afferent dendrites of the auditory nerve. These findings align with a computational evaluation conducted within a biophysical model of membrane currents, demonstrating an unexpectedly immense postsynaptic potential of the IHC ribbon synapse with an amplitude of 400pA[1].

Regarding the longer neural transmission time in this model compared to the I-III inter-peak latency, peak I seemingly occurred after the onset of primary neural activity. This observation suggests that the recorded I' wave in ABR is the result of IHC postsynaptic currents in type I spiral ganglion cells (46). Consequently, the absence or reduction of the I' wave amplitude and the symptoms of synapse dysfunction open a window to identifying cochlear synaptopathy.

The hypothesis

The disconnection of LSR auditory afferent fibers and IHCs is established as the primary cause of cochlear synaptopathy, supported by immunohistological investigations in animal models (15, 47) and autopsy findings in human subjects (48). Currently, the peak I amplitude is recognized as a potential biomarker for cochlear synaptopathy (39), supported by its correlation with histological findings in animal studies (49); however, it does not provide a comprehensive understanding of synaptic function(38). Conversely, the discrepancies in research findings—whether supportive (50, 51) or contrary (37, 52-55) to the association between this index and speech performance— pose a significant challenge to the generalizability of this correlation in human subjects(39, 56). Demographic variables (30, 57) and the variability associated with wave I may influence the results. Moreover, discrepancies between the fibers contributing to the wave I response and those vulnerable to cochlear synaptopathy may elucidate the absence of correlation observed across multiple studies (39). Previously, the greater contribution of HSR fibers to wave I generation (15) was noted due to the higher synchrony with stimulus onset (16). Cochlear synaptopathy may be identified by a tool capable of indirectly representing synaptic function as the site of lesion associated with noise-induced cochlear synaptopathy.

The application of the paired-click paradigm to assess temporal resolution (44) and nerve recovery time (38, 58, 59) has bolstered the hypothesis regarding its efficacy in evaluating synaptic function, leading to its exploration in recent studies on synaptopathy (38, 39, 43). While recovery time has emerged as a significant tool for assessing the auditory system's temporal resolution (44), its ability to accurately reflect synaptic function is questionable (58). In these investigations, efforts have been undertaken to record the EPSPs arising from synaptic activity by leveraging both the refractory period and short-term adaptation. Since previous studies have suggested a significant role of EPSP in eliciting the I' wave through the paired-click stimulation paradigm in ABR (42) and the presence of this peak at the synapse has been shown using computer modeling (46), I' wave is proposed as an indicator of synapse function and, consequently, a biomarker for the identification cochlear synaptopathy. Hence, in general, at least in people with a normal hearing threshold, the I' potential recorded by the standard clinical tools appears to represent the summation of the EPSP activity in the postsynaptic membrane and may illustrate the function of cochlear synapses.

Due to the importance of the results of synaptopathy in social relations, a test capable of evaluating EPSP has the potential to indirectly estimate the function of the ribbon synapse and thus identify cochlear synaptopathy. Emphasizing the

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histological and advanced imaging findings of synaptic ribbon pathologies in cochlear synaptopathy, we propose the I' wave as the probable choice for diagnosing this pathology. Accordingly, this hypothesis aims to introduce the I' wave as a possible indicator of cochlear synaptopathy.

Evaluation of the hypothesis

The initial phase of investigating this hypothesis involves exploring the correlation between the lack or decrease of the amplitude of the I' wave with the paired-click paradigm and histological findings indicating synaptic loss or damage in preclinical studies. Subsequently, a study that examines the correlation between clinical manifestations of cochlear synaptopathy—such as challenges in speech perception in noisy environments—and reduced I' wave amplitude in high-risk individuals would substantiate the hypothesis that I' wave may serve as a significant biomarker for the identification of cochlear synaptopathy, at least in normal hearing individuals.

In conclusion

Given that it is feasible to record I' wave using clinical ABR devices and standard transducers, it is necessary to augment the capabilities of this non-invasive and readily accessible instrument for broader application. To this end, it is essential to conduct studies aimed at elucidating the following critical clinical aspects: 1) Assessing the prevalence of the I' wave in populations categorized by gender, age, and hearing loss type, level, and configurations, 2) Analyzing the normative ranges for the amplitude and latency of the I' potential utilizing large sample sizes, and 3) Exploring individual, stimulus, and acquisition factors influencing I' recording across diverse populations.

Cochlear synaptopathy is defined as auditory dysfunction despite the normal hearing threshold, especially in challenging hearing situations (60). The association of cochlear synaptopathy with other common patient complaints, such as tinnitus and hyperacusis (49), along with the hypothesis that synaptopathy may be the primary cause of dysfunction in the elderly (2, 9, 20), highlights the need for an agreed-upon identifier. Such a tool may pave the way for studies designing preventive methods and potential treatments.

Considering the significant focus of research on cochlear synapse impairment in cochlear synaptopathy (12, 38), and in light of investigations that characterize I' wave as an EPSP generated by the synapse (41, 42, 46), this study presents the hypothesis that I' wave may serve as a reliable biomarker for identification of cochlear synaptopathy. Based on this hypothesis, the lack or decrease of the amplitude of the I' wave with the paired-click paradigm may represent a new possible diagnostic approach in cochlear synaptopathy. It is a simple, inexpensive, short-time test and a suitable option in clinical applications (48) that can be carried out with traditional types of equipment.

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Authors' Contribution

Azadeh Borna: Investigation, writing, review and editing. Abdollah Moosavi: Conceptualization (lead), review, and editing. Mehdi Akbari: Writing, review, and editing. Alireza Akbarzadeh Baghban: Writing, review and editing. Hamed Sajedi: writing, review, and editing.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could appear to influence the work reported in the paper.

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