Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2026**; 31(11): 55465
https://doi.org/10.31083/FBL55465

Short Communication

Preliminary Evidence for the Effect of Interferon on Metabotropic Glutamate Receptor Activity in the Vestibular Epithelium

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Academic Editor: Graham Pawelec
Submitted: 30 June 2026 Revised: 15 August 2026 Accepted: 1 September 2026 Published: 13 November 2026

Abstract

Background: The ototoxic effect of interferon (IFN) on the vestibular and auditory systems is associated with the cytokine's influence on the mediator functions of the vestibular and auditory epithelium. The function of the afferent glutamatergic synapse is mediated by the coupled action of ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs) and modulators of synaptic transmission. IFN has been shown to exert differential effects on iGluRs and to alter their functional interactions. This study focuses on the effect of IFN-α2b on mGluRs in the vestibular epithelium. **Methods**: To identify the role of IFN in the functioning of mGluRs, multiunit recording of impulse activity of the semicircular canal nerve fibers was performed under conditions of external perfusion of the vestibular apparatus. **Results**: IFN-α2b (10 ng/mL) depressed (±)-1-Aminocyclopentane-*trans*-1,3-dicarboxylic acid (*trans*-ACPD)-evoked responses (100 µM) during acute perfusion (main effect of treatment, repeated-measures analysis of variance (RM ANOVA): $F(2,14) = 8.55$, $p = 0.004$, $\eta^2 = 0.550$, $n = 8$. Post-hoc comparisons with Bonferroni correction: p (ACPD test vs. IFN+ACPD) = 0.033; p (IFN+ACPD vs. ACPD recovery) = 0.034). The amplitude of *trans*-ACPD-induced responses was restored after washing the vestibular apparatus with normal solution. **Conclusion**: IFN-α2b attenuates *trans*-ACPD-evoked, mGluR-mediated responses in the afferent glutamatergic synapse, suggesting that the cytokine may be regarded as a neuroimmunomodulator of mGluRs and participates in synaptic plasticity in the vestibular apparatus.

Keywords: interferon; vestibular epithelium; metabotropic glutamate receptors; neuroimmunomodulation

1. Introduction

Interferons (IFNs) are pro-inflammatory cytokines expressed and released by host cells in response to aberrant viral ribonucleic acid (RNA) or deoxyribonucleic acid (DNA). These protective properties of IFNs have been widely exploited in the treatment of multiple sclerosis, severe viral infections, and cancer [1,2,3]. High-dose IFN therapy is known to dysregulate key neurotransmitter systems in both the central nervous system (CNS) and peripheral nervous system, occasionally necessitating treatment withdrawal. Clinical data indicate that IFNs can cause acute hearing and balance loss [4,5]. Postural and balance disorders may be associated with dysfunction of both the central and peripheral components of the vestibular system. However, the nature of the ototoxic effect of IFN on the mediator systems of the inner ear structures has remained largely unexplored.

High sensitivity and plasticity of afferent synaptic transmission are achieved through the coordinated action of the glutamatergic, cholinergic, dopaminergic, and opioid systems, as well as endogenous modulators of synaptic transmission. Current literature indicates that active molecules of the immune system can modulate synaptic activity in the inner ear epithelium and alter the delicate balance of excitatory and inhibitory influences that ensure the perception and transmission of information from the auditory and vestibular organs to the CNS [6,7].

Our previous studies demonstrated for the first time that the afferent glutamatergic synapse can be a target for type I IFN. Using electrophysiological methods, we showed that IFN-α2b increased the frequency of background activity in afferent fibers but significantly reduced the amplitude of responses evoked by *L*-Glutamate (*L*-Glu) application relative to the new background activity level induced by IFN [7].

It is known that the high excitability and plasticity of the afferent glutamatergic synapse are ensured by the coupled activity of ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs) localized on pre- and postsynaptic membranes [8,9]. In-depth studies of the influence of IFN-α2b on various subtypes of iGluRs showed that IFN-α2b exerted diverse and complex effects on D, L-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and N-methyl-D-aspartate (NMDA) receptors. Specifically, IFN-α2b significantly increased kainate receptor activity but did not alter AMPA- and NMDA-induced responses during cytokine application. Unexpectedly, IFN-α2b exerted a delayed activating effect on kainate and AMPA receptors 15 minutes after co-exposure of kainate or AMPA and cytokine. Furthermore, IFN-activated AMPA receptors induced delayed

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significant changes in the amplitude of NMDA-evoked responses [10].

Since iGluRs and mGluRs are functionally linked and colocalized on the pre- and postsynaptic membranes of the glutamatergic synapse, this study aimed to investigate the effect of IFN-α2b on vestibular mGluRs.

2. Materials and Methods

The experiments were conducted *in vitro* during the autumn-winter period on adult male frogs (*Rana temporaria*) with a body length of approximately 5–7 cm and a weight of approximately 40–70 g. Frogs were wild-caught near St. Petersburg, Russia. Animals were kept in a dedicated refrigerator in containers with filtered standing water under a 12-h light/12-h dark photoperiod. The acclimatisation period was 14 days. All animals appeared healthy and showed no signs of disease prior to the experiments. 10 bone capsules with vestibular organs had been taken from various animals (10 frogs). All procedures were performed in accordance with the ethical principles set out in the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes. The protocol for obtaining the vestibular capsules was approved by the Ethical Committee of the Pavlov Institute of Physiology (approval No. 09/18, dated 18 September 2023). Each frog was anesthetized by immersion in 0.1% 3-aminobenzoic acid ethyl ester (MS-222) until all signs of respiratory activity ceased. Deep anesthesia was confirmed by absence of response to toe pinch. The animals were then decapitated. After decapitation, the destruction of the brain and spinal cord was performed. The bone containing the vestibular apparatus was dissected and transferred to the experimental setup.

The vestibular apparatus (the preparation) was then continuously perfused at room temperature with artificial perilymph solution of the following composition (in mM): NaCl 95, KCl 1.7, $NaHCO_3$ 3.4, $NaH_2PO_4 \cdot 2H_2O$ 0.5, $CaCl_2$ 1.8, $MgCl_2$ 0.6, glucose 2.5; the pH was adjusted to 7.4 (this solution is referred to as normal solution). The drugs used in the experiments were: (±)-1-Aminocyclopentane-*trans*-1,3-dicarboxylic acid (*trans*-ACPD) (Catalog No. 0187, Batch No. 20, https://www.tocris.com) and IFN-α2b (Altevir®, https://www.pharmapark.com) supplied in ampoules of 5,000,000 IU, purified by High-Performance Liquid Chromatography (HPLC) according to Sigma standard [7]. After purification, IFN-α2b was aliquoted and stored at 6–8 °C in the refrigerator. All necessary solutions in the required concentrations were prepared immediately before the experiment. The preparation was exposed to the drugs by continuous perfusion with normal solutions containing or lacking the test compounds. The perfusion rate was 1–1.5 mL/min. To ensure rapid access of the test substances to the synaptic contacts and to minimize diffusion barriers, the perfusion micropipette was positioned under visual control using a dissection microscope directly at the entry point of the nerve fibers enter the ampulla of the posterior semicircular canal.

Each vestibular apparatus was subjected to a control application of *trans*-ACPD (100 µM). The duration of *trans*-ACPD application was equal to the time required for the impulse frequency to reach its maximum and varied between 35 and 90 s. After a 15-min washout, a 2-min preperfusion with IFN-α2b (10 ng/mL) was performed, followed by application of *trans*-ACPD together with IFN-α2b. After another 15-min washout, *trans*-ACPD was applied again (ACPD recovery). In some experiments, to verify the triggering ability of the cytokine on the *trans*-ACPD-induced response, simultaneous perfusion of the synaptic region with a solution containing both IFN and the mGluR agonist *trans*-ACPD was used.

The effects of the test substances were assessed as the ratio of the peak firing frequency during drug application to the baseline activity level recorded during 1 min before perfusion.

Spike activity from the posterior semicircular ampullary nerve was recorded with a glass suction electrode, converted into rectangular pulses, and acquired continuously using custom-written software [11].

The effect of IFN-α2b on *trans*-ACPD-induced responses was assessed using Repeated Measures analysis of variance (RM ANOVA) with post-hoc comparisons adjusted by the Bonferroni correction. Although the Shapiro–Wilk test did not reject normality, all calculations were performed under the control of rank-based tests due to the small sample size (paired Wilcoxon signed-rank test). Statistical significance was set at $p < 0.05$. The sample size (n = 8–10 preparations) was based on our previous electrophysiological studies using the same experimental model [7,9], in which similar sample sizes were sufficient to detect significant effects. We present in the article the results of RM ANOVA. All calculations are performed using International Business Machines Statistical Package for the Social Sciences Software (IBM SPSS Software: version 26. Armonk, NY, USA. IBM Corp.). Graphs illustrating changes in *trans*-ACPD-evoked firing activity over time (before, during, and after IFN-α2b application) were generated after the experiment using Microsoft Excel LTSC MSO, Version 2408 (Build 16.0.17932.20910), Microsoft Corporation, One Microsoft Way, Redmond, WA 98052-6399, USA, https://www.microsoft.com, and software package SigmaPlot (Systat Software Inc. SigmaPlot 12.5: San Jose, CA, USA).

3. Results

The effect of IFN on mGluR activity was examined using simultaneous short-term exposure to the cytokine and the mGluR agonist *trans*-ACPD, as well as using a two-minute pre-application of IFN followed by *trans*-ACPD administration.

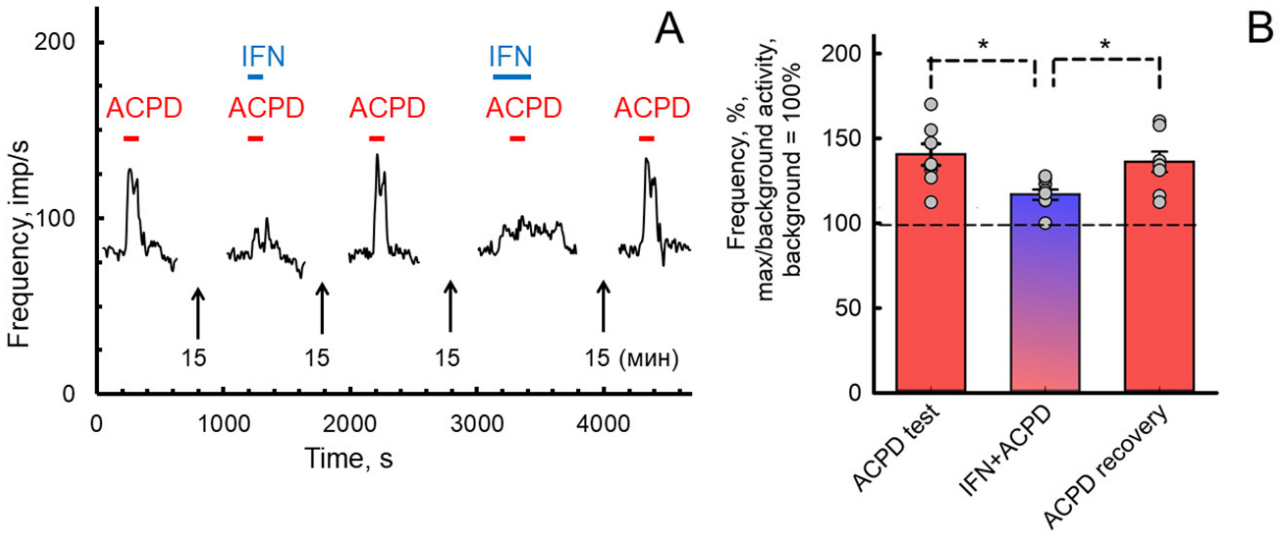


Fig. 1. Effects of interferon α2b (IFN; 10 ng/mL) on (±)-1-Aminocyclopentane-*trans*-1,3-dicarboxylic acid (ACPD)-evoked responses (100 µM) in the posterior semicircular ampullary nerve of the frog vestibular apparatus. (A) Original recording from a representative experiment: horizontal bars indicate the period of drug application; vertical arrows indicate 15-min washout with normal solution. The duration of *trans*-ACPD application was equal to the time required for the impulse frequency to reach its maximum (90 s). The IFN-α2b application time: first, a brief (90 s) simultaneous perfusion of IFN-α2b and *trans*-ACPD was performed. In the second case, the total duration of prolonged IFN-α2b application was 4 min 30 s, including the pre-perfusion time (2 min) and the time of the *trans*-ACPD-evoked response. (B) Summary data showing changes in *trans*-ACPD-evoked responses during prolonged IFN-α2b application: before cytokine exposure (ACPD test), during prolonged IFN exposure (IFN+ACPD), and after 15-min washout (ACPD recovery). The bar graph represents the ratio of the maximal *trans*-ACPD-induced response frequency to baseline activity (horizontal dashed line) (%), data are presented as mean ± SEM (n = 8 preparations). (*) Significant differences: RM ANOVA: F (2,14) = 8.547, p = 0.004, η^2 = 0.550. Post-hoc comparisons with Bonferroni correction: p (ACPD test vs. IFN+ACPD) = 0.033; p (IFN+ACPD vs. ACPD recovery) = 0.034.

To test the hypothesis that IFN-α2b can modulate mGluRs, the amplitude of *trans*-ACPD-induced responses was compared in the absence and presence of the cytokine. The effect of IFN-α2b (10 ng/mL, corresponding to 2600 IU/mL) on *trans*-ACPD (100 µM) -evoked responses was examined in 10 experiments. The following criteria were established for excluding experiments from statistical analysis: (1) the direction of the IFN effect, and (2) the availability of data at all stages of the experimental protocol. In 9 out of 10 experiments, IFN suppressed *trans*-ACPD-evoked responses after 2-min pre-perfusion. In one of the 10 experiments, IFN increased the *trans*-ACPD response (this experiment was excluded from analysis). In addition, in one of the remaining 9 experiments, the response to *trans*-ACPD (max/baseline) and the subsequent inhibition by IFN were exceptionally large, and ACPD recovery was not recorded. These data were excluded as outliers. The results of 8 experiments are presented in Fig. 1A,B.

IFN-α2b (10 ng/mL) exerted a significant inhibitory effect on trans-ACPD-evoked responses (RM ANOVA: F (2,14) = 8.547, p = 0.004, η^2 = 0.550). As shown in Fig. 1B, perfusion of vestibular end organs with the mGluR agonist *trans*-ACPD (100 µM) increased spike frequency to 140.46 ± 6.37% (mean ± SEM). After a 15-min washout with normal solution and a 2-min pre-application of IFN followed by *trans*-ACPD administration, *trans*-ACPD-evoked response amplitude was 116.84 ± 3.05%. A significant difference in *trans*-ACPD-induced responses was found between the test response and *trans*-ACPD-induced responses after 2 min of perfusion with the cytokine (Bonferroni post-hoc: p (ACPD test vs. IFN+ACPD) = 0.033; p (IFN+ACPD vs. ACPD recovery) = 0.034) (Fig. 1B). Following a 15-min washout of all test substances, the amplitude of *trans*-ACPD-induced responses was 136.10 ± 6.05%. The inhibitory effect of IFN-α2b on *trans*-ACPD-evoked responses was reversible, as indicated by the confidence intervals: the 95% CI for ACPD test (125.40 to 155.51) largely overlapped with that for ACPD recovery (121.80 to 150.41), the CI for the difference between means was (–8.893 to 17.603), confirming recovery of the response after washout.

To minimize the potential influence of IFN-α2b on background activity in the *trans*-ACPD-evoked response, simultaneous perfusion of the synaptic region with a solution containing both the cytokine and the mGluR agonist was used as a control. In this case, the perfusion time was

35–90 s; this duration was dictated solely by the time to peak of the *trans*-ACPD-evoked response. A similar inhibitory pattern of impulse activity was observed during long-term cytokine application, as shown in the representative recording (Fig. 1A).

4. Discussion

The mGluRs of vestibular end organs were thoroughly investigated by Guth and colleagues [12,13,14]. Messenger ribonucleic acid (mRNA) for mGluR1 has been detected in hair cells of the semicircular canals, utricle, and saccule, suggesting localization of mGluR1 on hair cell membranes. It has been proposed that hair cell mGluRs may function as autoreceptors, which can be activated to produce positive feedback enhancement of evoked, but not resting, transmitter release [12]. Using electrophysiological and immunocytochemical methods, both mGluR1 and mGluR2/3 were identified in the frog vestibular ganglion, suggesting postsynaptic localization of mGluRs. Importantly, the mGluR agonist *trans*-ACPD significantly potentiated AMPA- and NMDA-induced responses [9]. Activation of group I mGluRs has been shown to be associated with intracellular Ca^{2+} release from both inositol-1,4,5-trisphosphate (IP_3)-sensitive and ryanodine/caffeine-sensitive intracellular stores [13,14]. In summary, mGluRs in the vestibular organs are localized at both the pre- and postsynaptic membranes. Activation of these receptors triggers Ca^{2+} release from intracellular stores and prolongs the excitatory effects of AMPA and NMDA receptors.

mGluRs belong to the family of G protein-coupled receptors. Eight subtypes (mGlu1–8) are classified into three groups based on their sequence homology, post-receptor signaling, and pharmacology [15]. The signaling pathways triggered by mGluRs have been extensively characterized. Group I mGluRs couple via Guanine nucleotide-binding protein G(q) subunit alpha (Gq) to phospholipase C-β (PLC-β), resulting in the generation of IP_3 and diacylglycerol (DAG), which leads to mobilization of intracellular calcium and activation of protein kinase C (PKC). Group II (mGluR2 and mGluR3) and group III (mGluR4, mGluR6, mGluR7, and mGluR8) mGluRs couple via Guanine nucleotide-binding proteins subunit alpha ($G_{i/o}$) to negatively regulate adenylyl cyclase (AC), thereby reducing intracellular cyclic adenosine monophosphate (cAMP) levels, and also directly modulate ion channels and other downstream effectors through G protein beta-gamma subunit complex ($G\beta\gamma$) subunit-mediated signaling [16,17]. In the vestibular epithelium, cAMP plays an important role in modulating spontaneous afferent nerve firing in the semicircular canal [18].

Interferons are currently classified into three types according to the membrane receptors they bind [2]. IFN-α2b belongs to the type I IFN family (interferon-α, interferon-β). Its molecule contains two domains that determine its antiviral immune activity and opioid-like neuroregulatory effects [19]. Binding of type I IFN to its specific receptors—IFNAR1 and IFNAR2—initiates multiple canonical and non-canonical signaling cascades that are critical for the regulation of cellular functions [2]. The opioid-binding domain of type I IFN is involved in the modulation of physiological functions via μ-opioid receptors (MOR) [20,21]. In the glutamatergic synapse MOR have been identified on postsynaptic membrane in the *axolotl* vestibular apparatus [22].

We hypothesize that IFN may modulate group II mGluRs via suppression of AC, which is currently considered a critical mediator of neuroplasticity. Current data on the effects of interferons on AC activity are limited and have been obtained using different experimental models and time frames. It has been shown that the same target can be activated differently by various IFN types, which act through distinct receptors and trigger different signaling cascades [23]. The level of AC/cAMP can be modulated by both type I and type II IFNs. In the T84 cell line of intestinal epithelium, IFN inhibits AC expression and downregulates adenosine-mediated signaling. IFN suppressed cAMP and its downstream response induced by forskolin, the direct activator of AC [24]. At the same time, IFN-α2b has been shown to inhibit cAMP production, an effect that can be blocked by the opiate receptor antagonist naloxone [25]. Given that iGluRs and mGluRs are closely interconnected, we suggest that the classical cross-talk between iGluRs and mGluRs may be modulated in the vestibular apparatus. However, the detailed mechanisms underlying the effects of IFN on synaptic mGluRs remain to be elucidated.

5. Limitations

The study was performed on the isolated frog vestibular epithelium (an *in vitro* model) characterizing only type II hair cells with bouton synapse endings. The findings cannot be directly extrapolated to calyx synapse endings of type I hair cells in mammals, which are absent in amphibians and have a more complex synaptic organisation. Further studies are needed to fully understand the mechanisms of IFN action.

6. Conclusion

IFN-α2b suppresses mGluRs in the afferent glutamatergic synapse, suggesting that the cytokine may be regarded as a neuroimmunomodulator of mGluRs and participates in synaptic plasticity in the vestibular apparatus.

Abbreviations

AC, adenylyl cyclase; AMPA, D,L-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; cAMP, cyclic adenosine monophosphate; CNS, central nervous system; IFN, interferon; iGluR, ionotropic glutamate receptor; mGluR, metabotropic glutamate receptor; IP_3, inositol-1,4,5-trisphosphate; MOR, μ-opioid recep-

tors; NMDA, N-methyl-D-aspartate; *trans*-ACPD, (±)-1-Aminocyclopentane-trans-1,3-dicarboxylic acid.

Availability of Data and Materials

All data reported in this paper will be shared by the corresponding author upon request.

Author Contributions

IVR suggested idea and designed the research study. IVR and TVT performed the research and data analysis. EAV provided statistical data analysis. TVT and EAV designed the figure. IVR wrote the manuscript with input from all authors. All authors discussed the results and commented on the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All procedures were agreed with the ethical committee of the Pavlov Institute of Physiology (approval No. 09/18, dated 18 September 2023) and were performed in accordance with the ARRIVE guidelines and with the ethical principles set out in the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes.

Acknowledgment

The authors would like to thank O.V. Shamova, Corresponding Member of the Russian Academy of Sciences, Head of the Pathology Department of the Institute of Experimental Medicine, Saint-Petersburg, Russia, for support of the project and E.A. Protasov, Leading Engineer of this department, for interferon purification.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/FBL55465.

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