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OPEN PEER REVIEW

Impact of Pulsed Radiofrequency on Activated Dorsal Root Ganglion Neuronal Dynamics

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

3 comments · 3 Dec 2024 – 16 Dec 2024

Referee 1 Reviewer

MAJOR REVISION 3 Dec 2024

CONSORT Checklist Review
Question: Title and Abstract - Do the title and abstract provide a clear summary of the trial, including the experimental intervention and control?

Peer Review: The title and abstract clearly describe the study's focus on the effects of pulsed radiofrequency on dorsal root ganglion neurons, mentioning the comparison of different frequencies. The abstract summarizes the methods, results, and conclusions effectively.
Question: Introduction - Does the introduction clearly state the scientific background and rationale for the study?

Peer Review: The introduction provides a brief background on pulsed radiofrequency as a pain management intervention and highlights the gap in scientific data regarding frequency effects on DRG neuron physiology.
Question: Objectives - Are the specific objectives or hypotheses clearly stated?

Peer Review: The objective is clearly stated: to compare the cytosolic calcium, mitochondrial membrane potential, and neuronal activity dynamics of activated DRG neurons in response to different radiofrequency frequencies.
Question: Participants - Are the eligibility criteria for participants clearly defined?

Peer Review: The abstract does not specify eligibility criteria for participants as it is an in vitro study. Instead, it describes the experimental groups used.
Question: Interventions - Are the interventions for each group clearly described?

Peer Review: The interventions are well described, detailing the control group and the various treatments (NMDA, Ketamine, PRF at different frequencies) administered to the experimental groups.
Question: Outcomes - Are the primary and secondary outcome measures clearly defined?

Peer Review: The outcomes are clearly defined, focusing on cytosolic calcium dynamics, mitochondrial membrane potential changes, and neuronal activity.
Question: Sample Size - Is the sample size for each group provided?

Peer Review: The abstract mentions seven groups but does not specify the sample size for each group.
Question: Statistical Methods - Are the statistical methods used to compare groups for primary outcomes clearly described?

Peer Review: The abstract mentions the use of One-Way ANOVA for data analysis, with a significance level of $\alpha = 0.05$.
Question: Results - Are the results for each group, including the estimated effect size and its precision, clearly presented?

Peer Review: The results are presented with specific values for cytosolic calcium dynamics, mitochondrial membrane potential, and neuronal activity, including statistical significance.
Question: Conclusions - Are the conclusions supported by the results, and do they address the objectives?

Peer Review: The conclusions are supported by the results, indicating that 2 Hz normalizes neuronal activity, while 4 Hz does not, and both frequencies affect cytosolic calcium and mitochondrial membrane potential.
Categorization of Comments

Major Comments:
The abstract lacks specific details on the sample size for each experimental group, which is crucial for understanding the study's power and reliability.

Minor Comments:
The abstract could benefit from a more detailed description of the methodology, particularly regarding the experimental setup and conditions for the in vitro study.
Clarification on the rationale for choosing the specific frequencies (2 Hz and 4 Hz) would enhance the understanding of the study's design.

Associate Editor

MAJOR REVISION 16 Dec 2024

General Comments

The manuscript addresses an important topic in pain management: the effect of pulsed radiofrequency (PRF) at different frequencies on neuronal activity in dorsal root ganglion (DRG) neurons. The study offers valuable insights into the molecular and cellular mechanisms underlying PRF interventions, with implications for chronic pain therapies. However, the manuscript requires clarification and some improvements in writing, methodology reporting, and result interpretation to meet the standards of high-quality publication.

Strengths
Novelty: The study compares PRF at two commonly used frequencies (2 Hz and 4 Hz) for their effects on cytosolic calcium dynamics, mitochondrial membrane potential (MMP), and neuronal activity.
Methodology: Utilizes advanced techniques such as confocal microscopy, immunocytochemistry, and specific markers (e.g., Fluo-3/AM, pERK) to explore dynamic cellular processes.
Clinical Relevance: Provides molecular evidence supporting PRF at 2 Hz for pain management, a highly relevant finding for anesthesiologists and pain specialists.

Major Concerns

The abstract is dense, making it difficult to follow key findings. Simplifying it for clarity will improve reader comprehension.
Repetitive sections (e.g., theoretical background of PRF in “Background”) can be condensed without losing essential details.

Study Groups and Protocols: Details about NMDA and ketamine treatment are unclear. For example, why was ketamine only included in one group?
Was the 20 ms/10 ms duration for PRF exposure based on clinical relevance, prior studies, or preliminary experiments? This rationale should be explained.
Statistical Analysis: The manuscript reports statistical significance but lacks confidence intervals for key metrics. Adding these would improve reliability. It is unclear whether sample sizes (replicates) were sufficiently powered to detect differences.
Mechanistic Interpretation: The proposed mechanism linking PRF frequency, cytosolic calcium, MMP, and pERK intensity is logical but not sufficiently backed by cited literature. Incorporating references to related findings will strengthen the discussion.
A schematic of the experimental setup or intervention timeline would help readers understand the protocols more clearly.
Figures and Visual Data
Figures lack necessary annotations, making interpretation difficult. For instance, fluorescence images (e.g.,

pERK, MMP markers) should include labeled controls and activated models for better comparison.
Data variability is not always clear in the bar graphs (e.g., error bars and exact p-values are inconsistent).

Minor Concerns
Background: Avoid reiterating PRF's general benefits (lines 63–73) multiple times.
References: Some key studies, especially those on mitochondrial dynamics under PRF exposure, are outdated. Consider including recent literature to strengthen claims.
The limitations section acknowledges the need for dynamic pERK and MMP measurements but does not suggest concrete approaches for addressing this in future studies.

Recommendations

Revise the abstract to highlight the core findings and implications concisely.
Simplify the title for clarity, e.g., "Impact of Pulsed Radiofrequency on DRG Neuronal Dynamics: A Comparative Study of 2 Hz and 4 Hz."
Ensure all figures are self-explanatory with complete legends.
Present comparative results in a summary table (e.g., for calcium dynamics, MMP, and pERK across groups).
In the discussion, expand on the clinical implications of PRF at 2 Hz versus 4 Hz, specifically for chronic pain subtypes.
Discuss potential cellular or molecular adaptations that may explain why PRF at 4 Hz failed to normalize neuronal activity.

Editor-in-Chief MINOR REVISION 16 Dec 2024

Thank you for your contribution. Based on the reviewers' comments, you are recommended to make minor revisions before going to the next steps.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editorial Team
of JCMA

Thank you for your recommendation. We have made several revisions based on the editorial's recommendation. We highlight the revision in color.
We hope the revision meets the editor's satisfaction for publication.

Best regards,
Risriawan Muji Laksono, MD, FIPP, PhD

Reviewers' Comments:
Major Concerns
***1. The abstract is dense, making it difficult to follow key findings. Simplifying it for clarity will improve reader comprehension**.*
Repetitive sections (e.g., theoretical background of PRF in "Background") can be condensed without losing essential details.

Answer: We have revised the abstract and removed the repetitive section in the background

***2.** Study Groups and Protocols: Details about NMDA and ketamine treatment are unclear. For example, why was ketamine only included in one group?*

Answer: We have included the explanation in the methods

Was the 20 ms/10 ms duration for PRF exposure based on clinical relevance, prior studies, or preliminary experiments? This rationale should be explained.

Answer: It's based on clinical relevance. We have included the references

***3.** Statistical Analysis: The manuscript reports statistical significance but lacks confidence intervals for key metrics. Adding these would improve reliability.*

Answer: We have included the CI value

4. It is unclear whether sample sizes (replicates) were sufficiently powered to detect differences.

Answer: We have included the explanation.

5. Mechanistic Interpretation: The proposed mechanism linking PRF frequency, cytosolic calcium, MMP, and pERK intensity is logical but not sufficiently backed by cited literature. Incorporating references to related findings will strengthen the discussion.

Answer: We have rewritten the discussion

6. A schematic of the experimental setup or intervention timeline would help readers understand the protocols more clearly.

Answer: We have included the schematic setup (Figure 1)

7. Figures and Visual Data
Figures lack necessary annotations, making interpretation difficult. For instance, fluorescence images (e.g., pERK, MMP markers) should include labeled controls and activated models for better comparison.
Answer: We have revised the figure label and legend

8. Data variability is not always clear in the bar graphs (e.g., error bars and exact p-values are inconsistent).
Answer: We use the abcd notation to indicate the statistical difference between group from post Hoc test. We display the mean of every parameter in the new table with p-value from one-way ANOVA test.

Minor Concerns
9. Background: Avoid reiterating PRF's general benefits (lines 63–73) multiple times.
References: Some key studies, especially those on mitochondrial dynamics under PRF exposure, are outdated. Consider including recent literature to strengthen claims.
Answer: We have renewed the references

The limitations section acknowledges the need for dynamic pERK and MMP measurements but does not suggest concrete approaches for addressing this in future studies.

Answer: We have included measurement references in the limitation section

Recommendations
11. Revise the abstract to highlight the core findings and implications concisely.
Simplify the title for clarity, e.g., "Impact of Pulsed Radiofrequency on DRG Neuronal Dynamics: A Comparative Study of 2 Hz and 4 Hz."
Answer: We have revised the abstract

12. Ensure all figures are self-explanatory with complete legends.
Present comparative results in a summary table (e.g., for calcium dynamics, MMP, and pERK across groups).
Answer: We have revised the table and provided a summary table

13. In discussion, expand on the clinical implications of PRF at 2 Hz versus 4 Hz, specifically for chronic pain subtypes.
Answer: We have added more discussion

14. Discuss potential cellular or molecular adaptations that may explain why PRF at 4 Hz failed to normalize neuronal activity.

Answer: We have added more discussion

Major Comments:

- The abstract lacks specific details on the sample size for each experimental group, which is crucial for understanding the study's power and reliability.

  Answer: We have revised the abstract.

Minor Comments:

- The abstract could benefit from a more detailed description of the methodology, particularly regarding the experimental setup and conditions for the in-vitro study.

  Answer: We have revised the abstract.

- Clarification on the rationale for choosing the specific frequencies (2 Hz and 4 Hz) would enhance the understanding of the study's design.

  Answer: We have revised the abstract.

2 Revision 1

2 comments · 11 Jan 2025 – 11 Jan 2025

Associate Editor

ACCEPT 11 Jan 2025

The manuscript is well revised. I suggest that the manuscript be accepted.

Editor-in-Chief

ACCEPT 11 Jan 2025

Thank you for your great contribution.
I am happy to announce the acceptance of the manuscript.
Congratulations!