

Peer Review

Review of: "Orexinergic and Hypothalamic Dysfunction in Chronic Fatigue Syndrome: A Mechanistic Framework for Biomarker Discovery and Targeted Therapies"

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This paper, entitled "Orexinergic and Hypothalamic Dysfunction in Chronic Fatigue Syndrome: A Mechanistic Framework for Biomarker Discovery and Targeted Therapies," explores the role of hypothalamic and orexinergic dysfunction in Chronic Fatigue Syndrome (CFS/ME). The paper synthesizes evidence from neuroimaging, endocrine studies, and immunological analyses to examine how disruptions in orexin signaling and the hypothalamic-pituitary-adrenal (HPA) axis contribute to CFS. The focus on CFS biomarkers paves the way for a precision medicine approach aimed at improving diagnostic accuracy and treatment outcomes. However, the author concludes that longitudinal studies and interdisciplinary research are needed to validate proposed mechanisms and interventions.

In my opinion, this review provides a valuable synthesis of research on hypothalamic and orexinergic dysfunction in CFS, highlighting potential biomarkers and treatment strategies within an interdisciplinary dialogue. However, it would benefit from a more structured methodology and clearer result descriptions. Addressing these aspects would strengthen the paper's impact and utility for both researchers and clinicians.

Below, I provide specific concerns and suggestions for improvement:

The paper does not follow a traditional review structure. Instead of a clearly defined methods and results section, the author dives directly into detailed descriptions of:

- The Hypothalamus and Homeostatic Regulation (Section 2)

- Orexinergic signalling (Section 3)
- Hypothalamic dysfunction in CFS (Section 4)
- Orexinergic dysregulation in CFS (Section 5)
- Integrative models of Hypothalamic and Orexinergic Dysregulation in CFS (Section 6)
- Clinical Implications and Therapeutic Perspectives (Section 7)

While informative, this structure could be improved by integrating the background information into a more concise introduction and ensuring the core sections align with the stated research objectives.

Abstract and References

- The abstract refers to CFS/ME but does not define the ME acronym upon first use.
- Neuroimaging findings in the abstract are vague (“reduced hypothalamic volume and altered functional connectivity”); more specificity would improve clarity.
- The article would benefit from including more recent references on orexinergic system dysfunction in CFS.

Introduction

- The research question is clear and justified given existing knowledge. The author correctly highlights the diagnostic challenges of CFS due to the absence of definitive laboratory or imaging markers and the complex interplay of genetic, infectious, and immune dysfunctions.

However, the introduction could be better structured:

- The discussion of the social and economic cost of CFS (currently on page 3) could be moved earlier to establish the significance of the problem.
- The HPA dysfunction discussion (page 3) should be linked more explicitly to the diagnostic challenges discussed earlier on page 2.
- The introduction contains broad references to concepts that will be explored in the later sections (e.g., neuroimaging studies have also identified notable structural and functional brain changes, including reduced cortical volume, altered hypothalamic connectivity, and modifications in other brain regions, particularly in younger cohorts, Page 2).
- Again, when advising on the limited effectiveness of GET and CBT therapies, there is no reference to support this claim (Page 2).

Methods

-The process of study selection is not explicitly stated. A more structured methodology would help in assessing the validity of the findings. It is unclear whether there was a systematic search strategy for selecting reviewed studies. The inclusion criteria should be described.

Results

-Neuroimaging data on hypothalamic alterations should be more quantitatively detailed rather than broadly stating “altered functional connectivity.”

-More discussion is needed on whether orexinergic dysfunction is primary or secondary to inflammation and HPA dysregulation in CFS.

Discussion and Conclusions

-The discussion does well in synthesizing findings but should more clearly differentiate well-supported conclusions from hypothetical mechanisms requiring further validation.

-The conclusion emphasizes precision medicine approaches, but more detail on how these could be implemented in clinical settings is needed.

-The limitations of the reviewed studies (e.g., small sample sizes, heterogeneity in diagnostic criteria) are acknowledged but could be discussed in more depth. This part could benefit from a clear study selection and analysis.

Declarations

Potential competing interests: No potential competing interests to declare.