

Peer Review

Review of: "Proton Mechanisms of Neurotransmission and Calcium Signalling for Impulse Initiation, Development and Propagation"

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The review article **"Proton Mechanisms of Neurotransmission and Calcium Signalling for Impulse Initiation, Development and Propagation"** presents an ambitious and intellectually stimulating synthesis proposing an expanded role of protons as active contributors to neuronal excitability and synaptic transmission alongside classical ion-based mechanisms. The manuscript demonstrates extensive literature coverage across neurophysiology, cellular signaling, and membrane biophysics, and its integration of proton-calcium interactions provides a novel conceptual framework that may stimulate interdisciplinary discussion and future experimental exploration. The inclusion of biochemical pathways linking enzymatic hydrolysis, neurotransmitter metabolism, and proton generation represents a strong theoretical contribution. However, several limitations reduce the scientific robustness of the review. The manuscript frequently extrapolates from indirect or associative evidence to support broad mechanistic claims without sufficient critical evaluation of conflicting experimental data or alternative interpretations. The proposed hypothesis that protons may serve as primary initiators of neuronal firing, while intriguing, is presented with limited discussion of existing electrophysiological data that strongly supports sodium-channel-driven action potentials. Additionally, the methodology of literature selection is insufficiently described, lacking systematic review criteria or quality assessment of cited studies. Some sections contain speculative biochemical interpretations that would benefit from a clearer distinction between experimentally validated mechanisms and theoretical proposals. The review would be strengthened by incorporating quantitative experimental evidence, comparative analysis with established electrophysiological models, and clearer identification of testable hypotheses and translational implications. Overall, the article offers an innovative conceptual perspective that may

encourage further research but requires stronger critical balance and methodological transparency to enhance scientific rigor.

Declarations

Potential competing interests: No potential competing interests to declare.