An In Silico Study Unveiling the Biophysical Mechanisms of Cardiac Myocyte Membrane Potential Modulation by a Membrane-Targeted Photoswitch

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Abstract:

Optical stimulation is emerging as a promising alternative to conventional methods for both research and therapeutic purposes due to its advantages, such as reduced energy consumption, minimal invasiveness, and exceptional spatial and temporal precision.
Recently, we introduced Ziapin2, a novel light-sensitive azobenzene compound, as a tool to modulate cardiac cell excitability and contractility. The molecule proved to be effective in precisely regulating the excitation-contraction coupling process in both hiPS-derived cardiomyocytes and adult mouse ventricular myocytes (AMVMs). In the latter experimental model, we investigated the mechanism of action of Ziapin2, focusing in particular on its role in the initiation of action potentials (APs). In particular, experimental evidence suggest that stretch-activated channels (SACs) may respond to Ziapin2-induced mechanical inputs, contributing to light-driven AP generation. Despite our findings, further investigation is needed to fully clarify SACs role, given the complexity of the system and the lack of specific SAC blockers.

In this study, we aim to deepen the understanding of these mechanisms by proposing an enhanced computational model of murine AP that incorporates: i) the variation in membrane capacitance resulting from the trans-cis isomerization of the molecule in response to light stimulation; ii) stretch-activated ion channels (SACs) activated by membrane tension due to the thickness variation induced by Ziapin2.

Our numerical model accurately reproduces cell capacitance and membrane potential alterations induced by Ziapin2 photoisomerization. It elucidates the behavior observed experimentally in vitro in AMVMs, confirming the pivotal role of SACs in AP generation, particularly suggesting a significant involvement of selective Ca2+ channels.