Mechanistic Investigation of Cardiac Excitability Modulation by a Membrane-Targeted Photoswitch

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ABSTRACT

The use of light to modulate cellular activity offers a promising strategy in cardiac research, enabling precise spatial control with minimal invasiveness. Ziapin2, a membrane-targeted azobenzene derivative, has emerged as a potent tool for the light-mediated modulation of excitation-contraction coupling (ECC) in human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) [1,2]. This compound induces mechanical changes in membrane thickness upon light stimulation, resulting in alterations in membrane capacitance (Cm) that lead to shifts in membrane potential and subsequent action potential (AP) generation.

While a robust physical model has been proposed, the underlying biophysical mechanisms remain incompletely understood. To advance our understanding, we investigated the effects of Ziapin2 in a more mature cellular model—adult mouse ventricular cardiomyocytes (V-CMs). By combining standard electrophysiological techniques with advanced computational modeling, we explored the mechanism of Ziapin2 action in greater depth. Our in vitro experiments demonstrate that Ziapin2 can effectively modulate ECC in mature V-CMs without disrupting the primary sarcolemmal ion transporters and receptors. Furthermore, we established a mechanistic link between Ziapin2-induced modulation of membrane thickness and light-evoked AP firing, identifying the activation of stretch-activated ion channels (SACs) as a critical component through pharmacological inhibition studies [3].

These experimental findings were corroborated by mathematical simulations incorporating changes in Cm and SAC activation resulting from Ziapin2-induced membrane tension [4].

Collectively, our results provide novel insights into the biophysical basis of Ziapin2 function, highlighting its potential as a precise, non-invasive optomechanical tool for regulating cardiac electrical activity.

REFERENCES

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