INVESTIGATING THE MECHANISM OF CARDIAC CELL EXCITABILITY MODULATION BY A MEMBRANE-TARGETED PHOTOSWITCH

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The use of light to control cellular activity presents a promising approach in cardiac research due to its precise stimulus localization and minimal invasiveness. Ziapin2, a membrane-targeted azobenzene compound, has already been identified as an effective tool for light-driven modulation of excitation-contraction coupling (ECC) in hiPSC-derived cardiomyocytes. Its mechanical photomodulation of membrane thickness leads to changes in membrane capacitance (Cm), which are linked to membrane potential alterations that trigger action potential (AP) generation. Despite a robust physical interpretation, a detailed biophysical explanation of this process remains under investigation. To further explore this, we tested Ziapin2 in a more mature model: adult mouse ventricular cardiomyocytes (V-CMs). Using standard electrophysiological techniques and enhanced computational models, we delved deeper into the biophysical mechanisms. Our *in vitro* results demonstrate that Ziapin2 can photomodulate ECC in mature V-CMs without affecting the main transporters and receptors located within the sarcolemma. Furthermore, we experimentally established the connection between Ziapin2-induced membrane thickness modulation and light-induced AP firing by showcasing the pivotal role of stretch-activated ion channels (SACs) through pharmacological blockade. Our experimental findings were successfully supported by mathematical simulations, incorporating Cm changes and SACs activation due to membrane tension caused by Ziapin2-induced thickness modulation.
Together, these results enhance our understanding of the biophysical processes involved, shedding light on the mechanism of action of Ziapin2 as a novel, precise, and non-invasive tool for controlling cardiac electrical activity.