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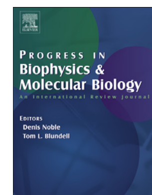

Review

# Cardiac applications of optogenetics

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In complex multicellular systems, such as the brain or the heart, the ability to selectively perturb and observe the response of individual components at the cellular level and with millisecond resolution in time, is essential for mechanistic understanding of function. Optogenetics uses genetic encoding of light sensitivity (by the expression of microbial opsins) to provide such capabilities for manipulation, recording, and control by light with cell specificity and high spatiotemporal resolution. As an optical approach, it is inherently scalable for remote and parallel interrogation of biological function at the tissue level; with implantable miniaturized devices, the technique is uniquely suitable for *in vivo* tracking of function, as illustrated by numerous applications in the brain. Its expansion into the cardiac area has been slow. Here, using examples from published research and original data, we focus on optogenetics applications to cardiac electrophysiology, specifically dealing with the ability to manipulate membrane voltage by light with implications for cardiac pacing, cardioversion, cell communication, and arrhythmia research, in general. We discuss gene and cell delivery methods of inscribing light sensitivity in cardiac tissue, functionality of the light-sensitive ion channels within different types of cardiac cells, utility in probing electrical coupling between different cell types, approaches and design solutions to all-optical electrophysiology by the combination of optogenetic sensors and actuators, and specific challenges in moving towards *in vivo* cardiac optogenetics.

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## 1. Introduction

Cardiac electrical activity is the product of a well-orchestrated system of functionally-distinct and spatially-distributed cells within the heart. Full understanding of the role of these distinct structures in normal and pathological conditions has been hindered due to lack of tools to selectively manipulate them *in vivo*, independently, and with high spatiotemporal resolution. Optogenetics (Boyden et al., 2005; Deisseroth et al., 2006; Nagel et al., 2005), the genetic modification of mammalian cells and tissues by microbial opsins (light-gated ion channels and pumps), offers potential solutions. This new method allows for cell-selective and spatiotemporally precise optical control of biological function, including manipulation of membrane voltage, intracellular concentrations, receptor control, gene expression etc. Over the last decade, optogenetics has been used widely in neuroscience to probe brain function in health and disease (Mattis et al., 2012; Yizhar et al., 2011). As a versatile optical interrogation tool, optogenetics is likely to have a similar impact on cardiac research, particularly cardiac electrophysiology, arrhythmias, cell signaling, and drug discovery (Ambrosi and Entcheva, 2014b; Boyle et al., 2014; Entcheva, 2013).

When expressed in mammalian cells, the microbial opsins at the core of optogenetics, used to modulate membrane voltage, can produce either depolarizing (excitatory) or hyperpolarizing (inhibitory) currents. Excitatory opsins, such as channelrhodopsin2 (ChR2) (Nagel et al., 2003), can provide currents sufficient for triggering action potentials, whereas inhibitory opsins, such as Archaerhodopsin (Arch) and Halorhodopsin (Halo), can suppress activity (Chow et al., 2010). Upon illumination with the appropriate wavelength, depending on the channel, molecules flow passively with (ChR2 – cations) or are actively pumped against (Arch – $H^+$;

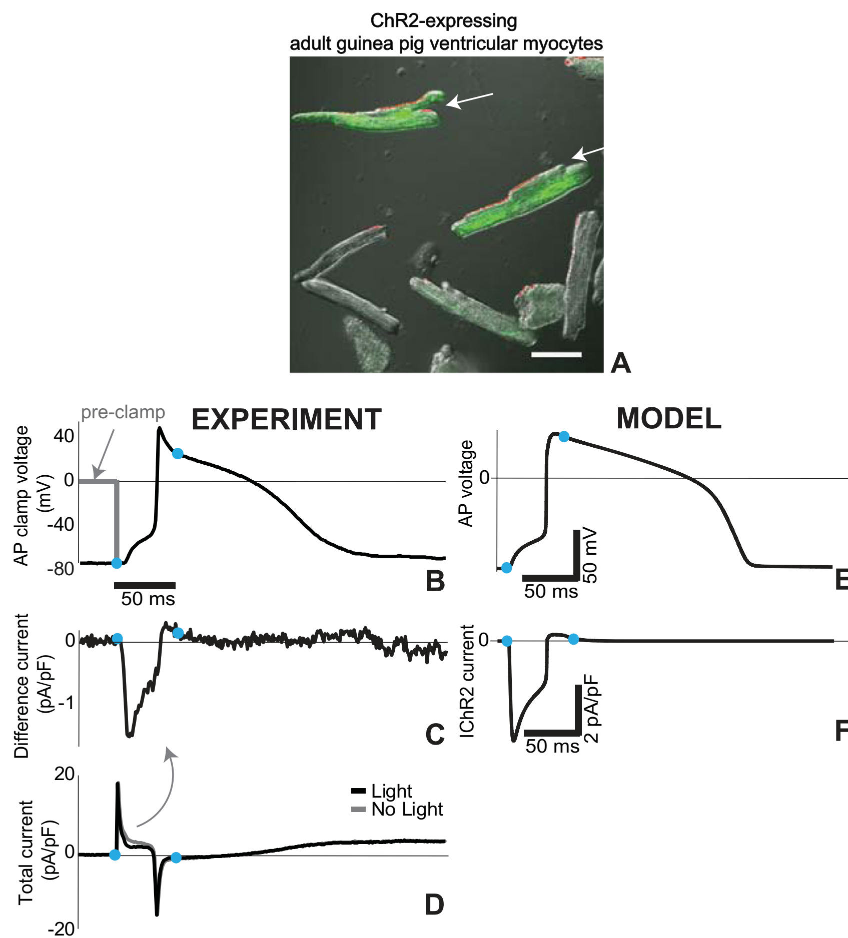


**Fig. 1. ChR2 current during the cardiac action potential via AP clamp. A**. Adult guinea pig ventricular cardiomyocytes after 48 h of viral infection with Ad-ChR2(H134R)-eYFP, green fluorescence indicates ChR2 expression; scale bar is 50 µm. Experimental (**B**–**D**) and modeling (**E**–**F**) traces for guinea pig ventricular cells. **B**. Optically-triggered action potential (50 ms pulse at 470 nm, 1.5 mW/mm$^2$) used for the AP clamp; dotted line indicates the voltage clamp conditions upon application of the waveform; blue dots indicate the beginning and end of the optical pulse. **C**. Extracted $I_{ChR2}$ as the difference current from the total current traces (panel **D**) recorded in dark conditions and with a light pulse. **E**. Analogous optically-triggered action potential in a model of a guinea pig ventricular cell. **F**. The underlying $I_{ChR2}$ according to the model. Reproduced with permission from (Williams et al., 2013).

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