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DEVELOPMENT OF A TECHNIQUE FOR NONINVASIVE CARDIAC PACING BASED ON THERMOSENSITIVE CHANNELS *

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Abstract

We have delivered the human TRPV1 thermosensitive cation channel gene into the culture of mouse neonatal cardiomyocytes and into the heart of an adult mouse. This made it possible to control the activity of the samples studied using short thermal pulses. We have successfully demonstrated the stimulation of both isolated cells in vitro and a whole heart in vivo, confirming the effectiveness of the approach.

Cardiac arrhythmias represent a major global health burden, with bradyarrhythmias being particularly life-threatening [1]. While implantable pacemakers and cardioverter-defibrillators remain the gold standard for treatment, these devices are associated with significant complications, including surgical risks, infections, lead dislodgement, and the need for periodic battery replacements. Recent studies report major complications in 8.2 % of patients within 90 days post-implantation [2], highlighting the urgent need for alternative therapeutic approaches. Emerging gene- and cell-based therapies offer promising solutions, with thermogenetics representing a particularly innovative strategy for cardiac rhythm modulation [3, 4].

In this study, we developed a thermogenetic pacing system utilizing the human transient receptor potential vanilloid 1 (TRPV1) channel, a heat-sensitive cation channel naturally present in mammalian tissues. Using adeno-associated virus (AAV) vectors carrying cardiac-specific promoters, we achieved the targeted expression of TRPV1 in both isolated cardiomyocytes and intact mouse hearts. Our results demonstrate that short pulses of infrared (IR) laser illumination can reliably induce action potentials in TRPV1-expressing cardiomyocytes in vitro, with activation kinetics closely matching natural pacemaker activity.

To evaluate the efficacy of thermopacing, experiments were conducted using optical mapping with calcium- and voltage-sensitive dyes. The performed experiments (in vitro –cultured neonatal mouse cardiomyocytes; in vivo — perfused mouse heart/thin mouse heart slices) demonstrated that the developed thermopacing method provides sufficient spatial (1.8–2.2 mm) and temporal (4 Hz) resolution. Optical mapping experiments confirmed that thermogenetic pacing preserves normal wave propagation patterns to electrical pacing. Additionally, issues such as calcium overload in cells during prolonged thermopacing were investigated.

Based on the obtained results, it was concluded that tissue parameters (conduction velocity) and electrophysiological parameters (action potential duration) under thermopacing do not differ from those observed with standard cardiac tissue stimulation. This confirms that thermogenetics represents a viable alternative to traditional cardiac pacing technologies, offering advantages such as specificity, minimally invasive application, and reduced risk of long-term complications. Further development of this technology may lead to novel therapeutic strategies for cardiac rhythm control, particularly in high-risk patients prone to complications associated with conventional devices.

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