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Review

Drugs that interact with cardiac electro-mechanics: Old and new targets for treatment

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Abstract

The concept of mechano-electrical feedback was derived from the observation that a short stretch applied to the beating heart can invoke an electrical response in the form of an afterdepolarization or a premature ventricular beat. More recent work has identified stretch-activated channels whose specific inhibition might help to treat atrial fibrillation in the near future. But the interaction between electrical and mechanical function of the heart is a continuum from short-term (within milliseconds) to long-term (within weeks or months) effects. The long-term effects of pressure overload have been well-described on the molecular and cellular level, and substances that interact with these processes are used in clinical routine in the care of patients with cardiac hypertrophy and heart failure. These treatments help to prevent lethal arrhythmias (sudden death) and potentially atrial fibrillation. The intermediate interaction between mechanical and electrical function of the heart is less well-understood. Several recently identified regulatory mechanisms may provide novel antiarrhythmic targets associated with the ''intermediate'' response of the myocardium to stretch.

Keywords: Arrhythmias; Mechano-electric feed back; Hypertrophy; Hypertension; Sudden death; Atrial fibrillation; Mechanism; Calcium; Action potential; Fibrosis; Cell–cell adhesion

Contents

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1. Introduction

The concept of mechano-electric feedback was derived from the observation that a short stretch applied to the beating heart can invoke an electrical response in the form of an afterdepolarization or a premature ventricular beat (Schütz, 1931, 1934; Zabel et al., 1996a). The elucidation of the pathophysiological substrate behind this phenomenon has resulted, among other things (Franz, 1996), in the characterization of biological peptides that specifically block stretch-activated channels in cardiomyocytes, a novel type of treatment for atrial fibrillation (Bode et al., 2001, see related article in this issue).

While this novel type of antiarrhythmic therapy for mechano-electric feedback awaits clinical exploration, the interaction between mechanical load and electrical properties of the myocardium is influenced by a continuum of short-term and long-term effects. In this broader sense, cardiac electro-mechanics describe the regulatory processes that adapt the electrical and the resulting contractile function of the heart to the demand needed for adequate blood supply of the body. Such adaptational processes are key to training, optimal cardiac performance, and ultimately to survival. Excessive work load demands, simultaneous (accidental) activation of several such processes, or a genetic susceptibility that makes an individual prone to abnormal response to pressure can cause unphysiological forms of cardiac adaptation to stretch. Such "feedback gone wrong" is one of the relevant causes for polymorphic ventricular and atrial arrhythmias, manifesting as the clinical entities sudden cardiac death and atrial fibrillation.

This review discusses the known effects of drugs that may be useful to modulate the myocardial response to short-term and long-term mechanical overload. The paper will close with the surprising observation that relevant mechanisms and potential drug targets that may underlie the "intermediate" response to the myocardium to stretch, a multifaceted signaling cascade that occurs within seconds to hours during myocardial stretch, have been less well-studied. We end the paper with the suggestion of potential new targets for treatment of unwanted, proarrhythmic effects of cardiac electro-mechanics.

2. The immediate response to stretch

Adequately timed short stretch pulses can acutely depolarize the myocardial membrane within milliseconds and give rise to afterdepolarizations and, if such a depolarization reaches a certain voltage threshold, cause a new action potential. This old concept has been well-described after the advent of high-precision piston pumps that allowed to alter left ventricular pressure within milliseconds in the isolated, beating heart (Zabel et al., 1996a) (see Fig. 1). These membrane depolarizations are caused by cation influx through *stretch-activated channels*, non-specific ion channels that open upon mechanical stretch. An expected effect of these channels