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The control of cardiac ventricular excitability by autonomic pathways☆

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ABSTRACT

Central to the genesis of ventricular cardiac arrhythmia are variations in determinants of excitability. These involve individual ionic channels and transporters in cardiac myocytes but also tissue factors such as variable conduction of the excitation wave, fibrosis and source-sink mismatch. It is also known that in certain diseases and particularly the channelopathies critical events occur with specific stressors. For example, in hereditary long QT syndrome due to mutations in KCNQ1 arrhythmic episodes are provoked by exercise and in particular swimming. Thus not only is the static substrate important but also how this is modified by dynamic signalling events associated with common physiological responses. In this review, we examine the regulation of ventricular excitability by signalling pathways from a cellular and tissue perspective in an effort to identify key processes, effectors and potential therapeutic approaches. We specifically focus on the autonomic nervous system and related signalling pathways.

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Contents

(See Table 1.)

1. Introduction

An array of ion channels and transporters determine the excitable properties of the heart. This can be assessed in a variety of ways from single cell studies using patch clamping and imaging, field potentials measured using electrode arrays from the surface of cardiac tissue through to measurement in the whole animal using electrocardiography. This normal electrical activity of the heart can become disordered and lead to cardiac arrhythmia. In the ventricle this is particularly critical as the activity can become sufficiently chaotic to lead to sudden cardiac death. The electrical activity of the heart can be modulated through hormonal signalling pathways particularly the two arms of the autonomic nervous system. For example, it is known that exercise can provoke arrhythmic events in hereditary channelopathies and that common cardiac pathologies such as heart failure can lead to a sympathovagal imbalance and may further enhance the predisposition to arrhythmia.

There has been a substantial body of important work over the last fifty years dissecting out the regulation of individual ion channels and currents in cardiac ventricular myocytes. These studies have often

Abbreviations: AP, action potential; APD, action potential duration; CPVT, catecholaminergic polymorphic ventricular tachycardia; CamKII, calcium calmodulin dependent kinase II; ERP, effective refractory period; ICD, implantable cardiac defibrillator; "I_x" where x is a specific identifier for the current, ion channel currents; IP_3, inositol trisphosphate; LQTS, long QT syndrome; LTCC, L-type calcium currents; NO, nitric oxide; NOS, nitric oxide synthase; PKA, protein kinase A; PKC, protein Kinase C; SA and AV, sinoatrial and atrioventricular respectively.

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Table 1
A Table summarising a potential consensus from the literature (see text for details and references) of the regulation of ion channels and the sodium-calcium exchanger by key signalling pathways related to autonomic modulation.

Current	Molecular composition	β-adrenergic regulation	α1-adrenergic regulation	Muscarinic receptor regulation	Nitric oxide signalling	CamKII signalling	Other
I_{Na}	SCN5A + β-subunits	Increases current and channel translocation	Not clear	Not clear	Not clear	Not clear	Ca^{2+} is inhibitory probably by direct pore block
L-type calcium current (I_{CaL})	Cav1.2 with $\alpha_2\delta$, β and γ subunits	Increased via PKA phosphorylation of Cav1.2	Not clear	M2 (and A1) antagonise but only with β-adrenergic activation	Inhibitory via PKG and direct channel nitrosylation	Increases via direct CamKII phosphorylation of Cav1.2. Responsible for Ca^{2+} dependent facilitation	High concentrations of Ca^{2+} such as occur on SR release result in channel inactivation
I_{to}	Kv4.2\4.3\KChiP	Not clear	Reduced	Not clear	Reduced	Not clear	Reduced by activation of angiotensin II receptor
I_{Kr}	KCNH2\KCNE2(?)	Not clear	Not clear	Not clear	Not clear	Not clear	Augmented by activation of angiotensin II receptor
I_{Ks}	KCNQ1\KCNE1	Increased via PKA phosphorylation of KCNQ1	Not clear (see other)	Not clear (see other)	Increased through direct channel nitrosylation	Not clear	Angiotensin II and other $G_{q\backslash 11}$ coupled receptors have been described to inhibit the current. Channel activity strongly dependent on PIP_2.
I_{KATP}	Kir6.2\SUR2A	Perhaps increased. Physiological significance unclear.	Not clear	Not clear	Not clear	Not clear	Inhibited by PIP_2 depletion via $G_{q\backslash 11}$ coupled receptor activation. Significance unclear.
I_{K1}	Kir2.1	Not clear	Not clear	Not clear	Not clear	No clear	No clear consensus on significant regulation
Sodium-calcium exchanger	NCX1	None	None	None	None	None	No significant regulation

occurred in single cells and the significance of the phenomena is not always clear for regulation in the whole heart. There has been less work in the whole heart and in man. In this review we consider how hormonal systems can modulate ventricular cardiac excitability. Specifically, we focus on processes in which there is a clear consensus of experimental evidence in single cells and consider how this links with tissue electrophysiology and arrhythmogenesis.

2. Ion channels and transporters determining ventricular excitability

A convenient cellular starting point is the ventricular cardiac action potential as illustrated in Fig. 1 together with how currents might be potentially modulated by increased beta adrenergic drive. We will briefly overview this area to set the scene but it is well known and has been reviewed before (Davis, van den Berg, Casini, Braam, & Mummery, 2011; Roden, Balser, George, & Anderson, 2002; Schmitt, Grunnet, & Olesen, 2014). We focus on the human action potential. It should be appreciated there are considerable species differences particularly between rodents and large mammals (Davis et al., 2011; Munroe & Tinker, 2015).

2.1. Sodium channels

The fast upstroke (phase 0) is mediated by rapid opening and subsequent inactivation of sodium channels. The pore forming cardiac isoform is SCN5A and there are a variety of beta isoforms that modulate the properties of the alpha subunit: at least two are present in the ventricle (Catterall, 2012). The alpha subunit consists of four groups of six transmembrane domains with voltage sensing and activation mediated by the S4 segment and inactivation by residues in the III-IV linker. It is possible other isoforms are present in the ventricle particularly in the t-tubular network (Westenbroek et al., 2013). Cardiac sodium channels are characteristically much less sensitive to tetrodotoxin than those present in central and peripheral nerves. It is also worth noting that sodium channels can continue to pass a small persistent inward current with prolonged depolarisation and that this can be increased in disease for example hereditary mutations in neuronal and cardiac sodium channels (Bennett, Yazawa, Makita, & George, 1995; Saint, 2008; The et al., 2006).

2.2. Transient outward K + current (I_{to})

There is transient repolarisation and notching of the action potential that is mediated by a group of potassium currents that rapidly activate and inactivate known as I_{to} ("transient outward"). $I_{to,f}$ is a fast transient K^+ current constituted of a complex of K_v4.2 and 4.3 and the beta subunit KChip2 (An et al., 2000; Dixon et al., 1996; Oudit et al., 2001). $I_{to,s}$ has slower kinetics, a more limited distribution probably only being present in myocytes from the ventricular septum and is likely constituted of K_v1.4 (London, Wang, Hill, & Bennett, 1998).

2.3. Calcium currents

Two major types of voltage-gated calcium channels are recognised in cardiac tissues namely L-type ("long-lasting") and T-type ("transient/tiny"). The L-type channel (LTCC) in the ventricle, is largely formed by Ca_v1.2 and can combine with ancillary subunits namely $\alpha_2\delta$, β and γ which increase alpha subunit expression, current density and alter the dynamics of activation/inactivation (Roden et al., 2002).

2.4. K^+ currents in terminal repolarisation

The potassium currents involved in terminal repolarisation are I_{Kr} and I_{Ks}. I_{Kr} is a rapidly activating and inwardly rectifying K^+ current that is formed by the complex of hERG (human ether-a-go-go related gene) together with perhaps a β subunit of the KCNE family (Abbott et al., 1999; Trudeau, Warmke, Ganetzky, & Robertson, 1995). I_{Ks} is

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