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Review

Mechano-sensitivity of cardiac pacemaker function: Pathophysiological relevance, experimental implications, and conceptual integration with other mechanisms of rhythmicity

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ABSTRACT

Cardiac pacemaker cells exhibit spontaneous, rhythmic electrical excitation, termed automaticity. This automatic initiation of action potentials requires spontaneous diastolic depolarisation, whose rate determines normal rhythm generation in the heart. Pacemaker mechanisms have been split recently into: (i) cyclic changes in trans-sarcolemmal ion flows (termed the 'membrane-clock'), and (ii) rhythmic intracellular calcium cycling (the 'calcium-clock'). These two 'clocks' *undoubtedly* interact, as trans-sarcolemmal currents involved in pacemaking include calcium-carrying mechanisms, while intracellular calcium cycling requires trans-sarcolemmal ion flux as the mechanism by which it affects membrane potential. The split into separate 'clocks' is, therefore, somewhat arbitrary. Nonetheless, the 'clock' metaphor has been conceptually stimulating, in particular since there is evidence to support the view that either 'clock' *could* be sufficient in principle to set the rate of pacemaker activation.

Of course, the same has also been shown for sub-sets of 'membrane-clock' ion currents, illustrating the redundancy of mechanisms involved in maintaining such basic functionality as the heartbeat, a theme that is common for vital physiological systems.

Following the conceptual path of identifying individual groups of sub-mechanisms, it is important to remember that the heart is able to adapt pacemaker rate to changes in haemodynamic load, even after isolation or transplantation, and on a beat-by-beat basis. Neither the 'membrane-' nor the 'calcium-clock' do, as such, inherently account for this rapid adaptation to circulatory demand (cellular Ca^{2+} balance changes over multiple beats, while variation of sarcolemmal ion channel presence takes even longer). This suggests that a third set of mechanisms must be involved in setting the pace. These mechanisms are characterised by their sensitivity to the cyclically changing mechanical environment, and – in analogy to the above terminology – this might be considered a 'mechanics-clock'.

In this review, we discuss possible roles of mechano-sensitive mechanisms for the entrainment of membrane current dynamics and calcium-handling. This can occur directly *via* stretch-activation of mechano-sensitive ion channels in the sarcolemma and/or in intracellular membrane compartments, as well as by modulation of 'standard' components of the 'membrane-' or 'calcium-clock'. Together, these mechanisms allow rapid adaptation to changes in haemodynamic load, on a beat-by-beat basis.

Additional relevance arises from the fact that mechano-sensitivity of pacemaking may help to explain pacemaker dysfunction in mechanically over- or under-loaded tissue. As the combined contributions of the various underlying oscillatory mechanisms are integrated at the pacemaker cell level into a *single* output – a train of pacemaker action potentials – we will not adhere to a metaphor that implies separate time-keeping units ('clocks'), and rather focus on cardiac pacemaking as the result of interactions of a set

Abbreviations: AP, action potential; BR, beating rate; Ca^{2+}, calcium; DD, diastolic depolarisation; HCN, hyperpolarisation-activated, cyclic nucleotide-gated; $I_{Ca,L}$, L-type calcium current; $I_{Ca,T}$, T-type calcium current; I_f, funny current (hyperpolarisation-activated depolarising current); I_K, outward potassium currents; I_{NCX}, sodium–calcium exchanger current; K^+, potassium; MDP, maximum diastolic potential; MSP, maximum systolic potential; Na^+, sodium; E_{rev}, reversal potential; RyR, ryanodine receptor channel; SAC_{NS}, cation non-selective stretch-activated channel; SAN, sino-atrial node; SERCA, sarco-/endoplasmic reticulum calcium-ATPase; SR, sarcoplasmic reticulum; V_m, transmembrane potential.

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of coupled oscillators, whose individual contributions vary depending on the pathophysiological context. We conclude by considering the utility and limitations of viewing the pacemaker as a coupled system of voltage-, calcium-, and mechanics-modulated oscillators that, by integrating a multitude of inputs, offers the high level of functional redundancy that is vitally important for cardiac automaticity.

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1. Introduction

Spontaneous mechanical activity of the heart is reported to have been recognised at least as far back as the second century, when Greek physician Claudius Galenus is credited with having noted that the heart continues to beat for an extended period of time when extracted from the chest (as cited by (Anglo, 1537)). It was not until the 19th century, however, that the seminal work of Gaskell (1882) confirmed the 'myogenic theory' of cardiac rhythm generation, originally proposed by Harvey (1651), and later supported by the work of von Haller (1757). Exploring the tortoise heart, Gaskell demonstrated rhythmicity as an intrinsic property of (in his view not fully differentiated) cardiac tissue and he proposed 'laws' of cardiac rhythm generation, in which he presaged that rhythmicity decreases with distance from the sinus, and that conductivity is inversely related to rhythmicity. This was followed by recognition of specific anatomical locations of cardiac automaticity in the mammalian heart, which are now known as the sino-atrial node (SAN, the primary structure responsible for initiation of the heartbeat (Keith and Flack, 1907)), and the atrio-ventricular node and Purkinje fibres (secondary and tertiary pacemaker regions (Tawara, 1906)).

A hundred years on, the cellular mechanisms of spontaneous pacemaker activity, and their relative contribution to pacemaking, are still a matter of debate (Brown et al., 1984; Lakatta and DiFrancesco, 2009; Rosen et al., 2012). It is clear, though, that cardiac pacemaking represents a robust and flexible system, integrating multiple contributors that allow adaptation to changes in circulatory demand.

In contrast to working cardiomyocytes in the atria and the ventricles, the action potential (AP) of cardiac pacemaker cells exhibits spontaneous diastolic depolarisation (DD; see Fig. 1). The rate of DD determines the time needed to take the trans-membrane potential (V_m) to the threshold for AP generation. Since V_m is an expression of the charge balance between the in- and out-side of the cell, changes in V_m *require* an imbalance between inward (depolarising) and outward (re- or hyperpolarising) trans-sarcolemmal currents, *i.e.*, a net-flux of charge across the membrane. DD will result from a 'surplus' in inward currents which, in a dynamic setting, may arise either from a relative increase in inward currents, or a decrease in outward currents (in the presence of sufficient inward current).

Early DD is a result of both, as outward potassium (K^+) currents (I_K) are reducing, in the presence of increasing inward currents, such as the electrogenic sodium–calcium (Na^+–Ca^{2+}) exchanger current (I_{NCX}), the hyperpolarisation-activated (*i.e.*, increasing in early diastole) 'funny' current (I_f; DiFrancesco, 1985), and any background conductances that carry inward currents, for instance the sodium (Na^+) background current (Noble et al., 1992). In contrast to the Na^+ background current, whose molecular nature is still under investigation, it is known that I_f is conducted by hyperpolarisation-activated cyclic nucleotide-gated (HCN) proteins, of which four isoforms have been identified in cardiac and neuronal tissue (Moosmang et al., 2001). Cardiac I_f is composed primarily of HCN4, and to a lesser degree of HCN2 and HCN1, in a species- and cell-type dependent manner (Barbuti et al., 2011; Scicchitano et al., 2012). Quantitative simulation has shown that these channels, even if one considers them as conductors of monovalent cations only (*i.e.*, K^+ and Na^+, although there is now evidence that they also conduct calcium, Ca^{2+}; Michels et al., 2008; Yu et al., 2007), are sufficient to give rise to cyclic changes in V_m (Noble et al., 1992). Their importance for pacemaking has been experimentally confirmed as HCN expression in non-pacemaking cells confers spontaneous activity (Li, 2012; Robinson et al.,