Supraventricular pacemaker activity in the canine heart: Contributions from HCN channels in control conditions and in a model of heart failure

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See also article by Zicha et al. [1] (the Nattel Research Group) (pages 472–481) in this issue.

An interesting and clearly presented paper from the Nattel Research Group [1] in this volume of *Cardiovascular Research* provides new evidence for the expression of three isoforms of hyperpolarization-activated cyclic nucleotide-gated ion channels (HCN) in the sinoatrial node and atria of the adult canine heart. These measurements have been made under control conditions, and in the setting of a model of congestive heart failure–tachycardia-induced sinus node dysfunction.

A major premise of this study is that although it is well-known that transmembrane ionic currents generated by HCN ion channels contribute to pacemaker activity, there appear to be significant species differences, and little information on this topic is available for the canine heart. The adult canine is a useful model for making control measurements and then studying selected pathophysiological paradigms which may be relevant to human clinical cardiac electrophysiology and to heart failure [2–5].

The immunohistochemical, molecular, and protein biochemical analyses in this paper show that in this canine model, myocytes from within the sinoatrial node region express the isoforms of this current which have been denoted HCN1, HCN2, and HCN4, with HCN2 and HCN4 predominating. Under control conditions, somewhat similar patterns of results are obtained from the right atrium. Interestingly, however, in preparations from animals in which congestive heart failure was induced by overdrive pacing, the pattern of HCN expression in the sinoatrial node showed a decrease in HCN2 and HCN4; while in the right atrium HCN2 was unchanged but HCN4 expression increased approximately 2-fold.

1. Previous findings

A slow time- and voltage-dependent hyperpolarization-activated inward current exhibiting approximately equal selectivity for monovalent cations was first identified in studies of pacemaker activity in the amphibian heart and in rabbit sinoatrial node (for review see [6,7]). In a series of very important papers which followed, DiFrancesco and his colleagues provided the original and extensive biophysical and pharmacological characterization of this current [8–10]. They also demonstrated that its amplitude and time course are modulated by noradrenaline and acetylcholine in ways which would be consistent with it being an important regulator of heart rate [8,9]. In addition, DiFrancesco et al. [8] have reported that the underlying (and very small unit conductance single channel activity) can be modulated significantly by a direct action of cyclic AMP as opposed to a cyclic AMP-mediated phosphorylation [10].

2. The role of If in normal pacemaker function

Uncertainty and controversy still exist regarding the very important issue of whether the current change generated by these HCN channels is in fact the major, or even a significant contributor to primary as opposed to secondary pacemaker activity. The molecular correlates for the macroscopic current, which is denoted If, or Ih, and the underlying cyclic nucleotide gated channel activity have been identified unequivocally [11–17]. These data show that in a normal
mammalian heart the current which has been denoted If is generated by channels which are formed by heteromultimers of the HCN2 and HCN4 families. Subsequent genetic manipulation of the synthesis or expression of these channels has resulted in additional evidence for the contribution of HCN2 and HCN4 to If in cardiac muscle. Insights into the way in which these transcripts can contribute to the observed and quite complex time- and voltage-dependent behaviour of these hyperpolarization-activated currents have also been obtained [18,19].

An unequivocal answer to the question whether and to what extent If contributes to pacemaker activity will require additional biophysical analyses directed toward determining the exact voltage dependence and kinetics of activation of the currents due to HCN channels. Further characterization of the ion selectivity and modulation by extra- and intracellular signaling pathways are also needed. Although substantial evidence exists on each of these points, few studies have been done under conditions which account for the sigmoid activation of this current and its complex deactivation. Both need to be studied in detail (c.f. [18,19]). Moreover, the way in which either noradrenaline or intracellular Ca$^{2+}$ can alter the magnitude of this current remains somewhat unclear. At present, it is apparent that If represents a class of ion channels that can contribute important current changes during pacemaker activity, it seems plausible that these channels do this mainly under the conditions of significant sympathetic drive, and have a less significant role under other circumstances.

The very small size of the current change due to HCN channels within the range of potentials which corresponds to pacemaker depolarization will mean that this physiological mechanism will need to be addressed using both experimental techniques (electrophysiology and molecular biology) and mathematical modeling. Comprehensive analysis of the single cell phenotype and the changes in pattern of expression of ion channels as a function of the exact anatomical location and/or alterations following autocrine or paracrine challenges will need to be done [20].

3. If in heart failure: ectopic supraventricular pacemaker activity

A further important issue raised by this paper [1] and by previous data, concerns the involvement of If in primary pacemaker activity in pathophysiological situations, e.g., congestive heart failure. In this setting, primary pacemaker activity can be slowed significantly or secondary pacemakers can arise as ectopic foci [4,5,21,22]. With respect to an involvement of HCN channel activity in these pacemaker responses, the Nattel et al. study [1] demonstrates a marked downregulation of the HCN2 and HCN4 channels in SA node, and a corresponding upregulation of HCN4 in atrial tissue. It is known that there is an increased tendency for supraventricular rhythm disturbances in the setting of congestive heart failure [21]. However, considerable additional work will be needed to link the changes in these or other ion channel transcripts to those abnormal patterns of electrical activity. It is plausible that change in either the amount of inward current or its pattern of expression (e.g., due to the abnormal activity of If) could significantly depolarize atrial myocytes, as a result of their relatively high input resistance and low safety factor for repolarization, c.f. [23,24]. The resting potential in the atrial myocardium is positioned at approximately $-70$ mV, i.e., near the foot of the activation curve for the macroscopic current, If. In the setting of congestive heart failure, increased adrenergic tone develops. As noted, the DiFrancesco group [9,10] has demonstrated that sympathetic stimulation or intracellular application of cyclic AMP, causes a marked shift of the activation curve for If. This change in the depolarizing direction could increase the extent of If activation. Further, the slow kinetics of deactivation of this current could result in cumulative activation of HCN channels at the high rates of firing commonly associated with atrial flutter or atrial fibrillation [25]. Under these conditions, the relatively high frequency electrical activity will result in repetitive activation of If and the underlying HCN channels will have insufficient time to deactivate in these short diastolic intervals. HCN channel activity will therefore manifest as what some could consider a steady-state inward current.

We can anticipate and look forward to additional work from the Nattel laboratory and other groups (e.g., [20]) who address these and other important mechanistic and functional questions concerning primary, secondary and ectopic cardiac pacemaker activity. This information will contribute to the growing interest in and impressive progress toward some tissue engineering approaches to ‘biological pacemakers’ [26–28].

References


