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Review article

Specificities of atrial electrophysiology: Clues to a better understanding of cardiac function and the mechanisms of arrhythmias

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ABSTRACT

The electrical properties of the atria and ventricles differ in several aspects reflecting the distinct role of the atria in cardiac physiology. The study of atrial electrophysiology had greatly contributed to the understanding of the mechanisms of atrial fibrillation (AF). Only the atrial L-type calcium current is regulated by serotonine or, under basal condition, by phosphodiesterases. These distinct regulations can contribute to I_{Ca} down-regulation observed during AF, which is an important determinant of action potential refractory period shortening. The voltage-gated potassium current, I_{Kur}, has a prominent role in the repolarization of the atrial but not ventricular AP. In many species, this current is based on the functional expression of $K_V1.5$ channels, which might represent a specific therapeutic target for AF. Mechanisms regulating the trafficking of $K_V1.5$ channels to the plasma membrane are being actively investigated. The resting potential of atrial myocytes is maintained by various inward rectifier currents which differ with ventricle currents by a reduced density of I_{K1}, the presence of a constitutively active I_{KACh} and distinct regulation of I_{KATP}. Stretch-sensitive or mechanosensitive ion channels are particularly active in atrial myocytes and are involved in the secretion of the natriuretic peptide. Integration of knowledge on electrical properties of atrial myocytes in comprehensive schemas is now necessary for a better understanding of the physiology of atria and the mechanisms of AF.

Contents

1. Introduction

The right and left atria are important regions of the heart with specific roles in cardiac physiology. They control the filling of the two ventricles during diastole. They also have an important endocrine function which is to secrete natriuretic peptide in response to physiological changes in blood volume. The two atria themselves differ remarkably in their roles and consequently by their electrophysiological properties. The right atrium accommodates the source of the cardiac pacemaker activity, the sino-atrial (SA) node, which is not the focus of this review [1]. The electrical activity of atrial myocytes is directly or indirectly involved in these physiological properties, probably explaining their specificities compared to the ventricles. A number of tachyarrhythmias originate from the atria, the most frequent being the atrial fibrillation (AF). For these reasons, the cellular and molecular bases of atrial electrophysiology have been extensively investigated. During cardiac surgery, a sample of the right atrial appendage can easily be obtained. Hence, a large part of our

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knowledge on cellular atrial electrophysiology arises directly from human heart. This does not lessen the otherwise large contribution provided by animal models.

The first information on the electrophysiology of human right atria was obtained with the microelectrode technique used to record action potential (AP) in muscle trabeculae [2]. A typical atrial AP has been described as characterized by a prominent plateau phase that activates at a relatively low level of membrane potential and is preceded by a deep notch. Since these early studies, most of the electrogenic systems underlying atrial AP have been described and their molecular basis identified.

1.1. Depolarizing currents: L-type calcium current and AF

Two main inward currents participate in the upstroke of atrial AP: the sodium and the L-type calcium currents. No T-type calcium current could be detected in human atrial myocytes [3]. It has been known for a long time that the $[dV/dt]_{max}$ of atrial AP is markedly lesser than that of the ventricle, on first glance indicating a lower I_{Na} due to lesser expression of Na_V subunits, which is supported by recent transcriptomic studies [4]. However, a report by Burashnikov et al. [5] shows a much higher I_{Na}-density in the atria compared to the ventricle, explained by a near to 100% sodium channel availability for the ventricle and around 20% for the atrium, at −80 mV. In cardiac myocytes, the main α subunit sodium channel isoform expressed is the TTX-resistant $Na_V1.5$. However, TTX-sensitive Na_V mRNA accounts for 16% of the sodium channel transcripts ($Na_V1.4 > Na_V1.3 > Na_V1.2 > Na_V1.1 > Na_V1.6$), contributing to 8% of the total I_{Na} [6]. The distribution of Na_V α- and β-subunits differs between ventricles and atria and could also contribute to the difference in current density [4].

The L-type calcium current (I_{CaL}) is the main depolarizing current involved in the plateau phase of the AP. I_{CaL} exhibits difference between the atrium and the ventricle mainly through its regulations by second messengers. For instance, a regulation of I_{CaL} by serotonin has been described only in atrial myocytes [7]. In atrial but not ventricular myocytes, phosphodiesterases (PDE) regulate I_{CaL} in the absence of β-adrenergic stimulation, indicating a basal production of cAMP and cGMP [8,9]. This basal production of nucleotides could reflect some feedback loop in the natriuretic peptide secretory process. These peptides bind to three different receptors. Two of which are membrane-bound guanylyl cyclases and are expressed in the right and left atria of primate hearts [10]. In human atrial myocytes, these receptors are functionally coupled to several ionic currents including the pacemaker [11] and the L-type calcium currents [12,13].

Either during AF or in dilated atria, there is a drastic reduction in I_{Ca} (~70%) which contributes greatly to the shortening of the AP or the refractory period or the formation of reentrant circuits (Fig. 1) [14–17]. It can be due to decreased number of calcium channel (Cav1.2) subunits [18–20] although this decrease was not consistently observed [21,22]. Alteration in the phosphorylation of calcium channels appears as an important mechanism of this current reduction. During AF or dilated atria, abnormally high sensitivity of I_{CaL} to β-adrenergic agonists has been observed, suggesting that calcium channels are in a dephosphorylated and silent state, and that they can be recruited upon β-adrenergic stimulation [13,16,21,23–25]. In dilated atria in a rat with heart failure, the down-regulation of I_{CaL} is caused by the intracellular accumulation of cGMP and PDE [23]. Natriuretic peptide could be responsible for the up-regulation of cGMP-dependent signaling pathway. [13,23,26]. For instance, patients with reduced atrial I_{CaL} and a dilated atrium display an increase in ANP plasma concentration (Fig. 1) [24]. Of note, a mutation in the gene coding ANP has been described in a familial form of AF. The mutant peptide, the plasma concentration of which is markedly enhanced, reduces the duration of the atrial potential duration [27]. Several phosphatases regulating calcium channels are up-regulated during AF and could also contribute to the down-regulation of I_{CaL} [22]. During AF, glutathione, an important modulator of cellular redox state that regulates I_{CaL} [28,29], is decreased while the redox state of calcium channels is altered [30].

In addition to its role in shaping the AP, I_{CaL} triggers the release of calcium from the sarcoplasmic reticulum (SR) and is thus a key effector for the activation of atrial contraction. The T-tubule system is poorly developed in the atria and a number of terminal cisternae of the SR are not associated with the plasma membrane (also named corbular or non-junctional SR). This distinct microarchitecture is associated with peripheral and central Ca^{2+} release during twitch contraction [31–33]. While the former calcium release component is gated by the calcium current, the latter is activated by the propagation of peripheral Ca^{2+} release. The respective physiological role of central and peripheral Ca^{2+} release is not yet clear. Notably, the extent of these low calcium releases differentially contribute to the passive and/or the active contractions of the atria. The high incidence of calcium-dependent triggered activities (delayed after depolarizations or DADs) in human atrial myocytes could be strengthened by the abundant corbular SR [34,35].

1.2. Repolarizing current: the predominant role of I_{Kur}

The human right atrial AP morphology can change considerably under various conditions and, can, for instance, transform into a

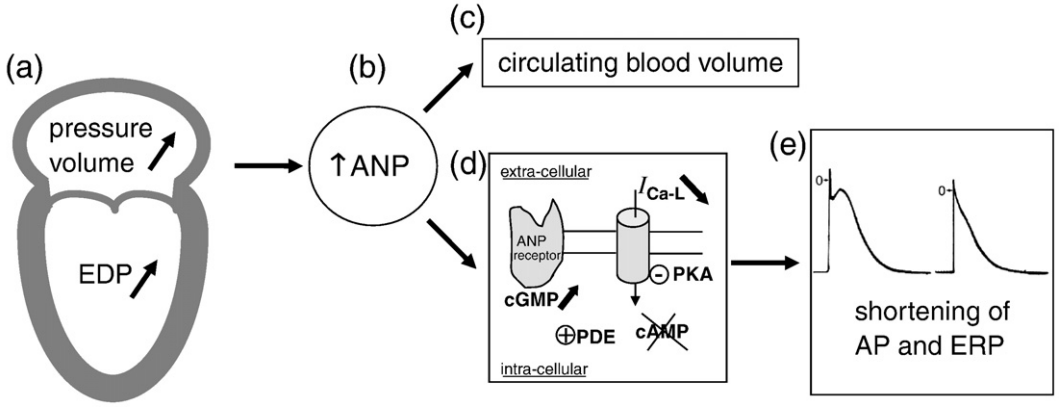

Fig. 1. Schema of a possible relationship between changes in the working conditions of the atrium and alterations of its electrical properties. (a) Increased end diastolic ventricle pressure (EDP) such as that which occurs during heart failure causes hemodynamic overload of the atrium triggering the secretion of the atrial natriuretic peptide (ANP) (b) which regulates blood volume (c). ANP also binds to its receptors, a particular guanylyl cyclases, resulting in the accumulation of cGMP, stimulation of phosphodiesterases (PDE), degradation of cAMP and decrease in I_{Ca} density (d), contributing to the shortening of the action potential duration and refractory period (e) (from refs. [13,16,23–25]).