Editorial

Atrial gap junction remodeling: Looking for lost gaps and orphaned connexins in three dimensions

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Received 19 July 2006; accepted 25 July 2006
Available online 1 August 2006

See article by Rucker-Martin et al. [22] (pages 69–79) in this issue.

1. Connexins and gap junction channel function in the heart

Gap junction channels are composed of members of a multi-gene family of proteins called connexins. These proteins are named by the abbreviation Cx followed by the molecular weight of the specific protein. Mammalian cardiac myocytes express Cx43, Cx45, and Cx40, the former being the major cardiac gap junction protein, which is expressed in atrial and ventricular myocytes as well as in selected regions of the atrioventricular conduction system [1,2]. Individual gap junction channels (also called connexons) formed by multiple connexin molecules exhibit distinct unitary conductance, pH and voltage dependence, and permeability to ions and small molecules as well as fluorescent dyes [3]. Regulation of the extent to which cardiac myocytes are electrically coupled by gap junction channels is complex and still not well understood [4,5]. In general, it appears that cells can rapidly (within minutes) change the number of functional channels at the cell surface through multiple mechanisms involving mobilization of intracellular connexin molecules to junctional plaques, internalization of junctional channels, changes in channel open probability and, potentially, changes in rates of connexin synthesis and degradation. Phosphorylation of multiple serine and tyrosine residues in the intracellular C-terminal domains has been shown to be important in Cx43 and Cx45 assembly into gap junction channels and in changes in channel function, intracellular translocation, and degradation [6]. Indeed, Cx43 can be phosphorylated on specific serine residues by mitogen-activated protein (MAP) kinases, protein kinases C (PKC) and A (PKA), and casein kinase I and on tyrosine residues by v-src and c-src [6–8]. However, the precise signaling mechanisms responsible for changing intercellular coupling in cardiac myocytes are incompletely understood.

2. Gap junction remodeling and electrical uncoupling in myocardial ischemia, cardiac hypertrophy and heart failure

Electrical uncoupling during ischemia is a complex phenomenon that involves closure of gap junction channels and changes in connexin phosphorylation and redistribution. Mechanisms responsible for initiating uncoupling during earlier stages of ischemic injury probably involve stress-activated signaling pathways causing changes in connexin phosphorylation. For example, the onset of uncoupling in no-flow ischemia in isolated perfused rat hearts is associated with progressive dephosphorylation of Cx43, accumulation of non-phosphorylated Cx43 in junctions, and translocation of Cx43 from junctions to an intracellular pool [9]. Nevertheless, the precise mechanistic relationships between channel closure, changes in phosphorylation, and intracellular translocation remain to be established. In contrast, early compensatory hypertrophic growth of cardiac myocytes appears to be associated with enhanced cell–cell communication. A recent in vitro study has shown that application of linear pulsatile stretch to cultured neonatal ventricular myocytes for only 1 h causes a 2-fold increase in Cx43 expression, associated with a 30% increase in conduction velocity [10]. Signaling pathways involving transforming growth factor β, vascular endothelial growth factor, and angiotensin II have been directly implicated in stretch-induced upregulation of Cx43 expression in cultured myocytes [11,12]. Finally, reduced Cx43 expression in gap junctions has been described in the hearts of patients with end-stage heart disease of diverse etiologies, including ischemia,
hypothesis, atrial fibrillation (AF), valvular abnormalities, and primary cardiomyopathies [13–15]. Diminished Cx43 expression in end-stage heart disease has also been associated with selective loss of larger gap junctions at the polar ends of cells [16]. Although little is known about the mechanisms responsible for changes in connexin expression and gap junction remodeling in chronic forms of heart failure, there may be a role for c-Jun N-terminal kinase (JNK), a stress-related protein kinase activated in response to injury caused by ischemia–reperfusion or hemodynamic overload.

3. Cardiac gap junction remodeling and lateral redistribution of connexins

A recently observed remodeling feature is lateral redistribution of gap junctions (also called “cellular lateralization”). Cellular lateralization occurs in ventricular myocytes during healing after myocardial infarction [17], with right ventricular hypertrophy secondary to pulmonary hypertension [18], in hypertrophic cardiomyopathy [19], and in human atria during aging [20] and after prolonged AF [14]. Interestingly, cellular lateralization has also been related to re-entrant ventricular tachycardia circuits that develop following premature stimuli during the healing stage of canine infarcts [21]. Although there is an association between inducibility of arrhythmias and cell lateralization of connexins, it is not clear what effect the cellular redistribution of gap junctions has on cell–cell transmission, nor what role the remodeled lateral distribution of gap junctions plays in altering conduction velocity at the macroscopic size scale. Thus, knowledge of the functional consequences of cellular redistribution of cardiac gap junctions is still quite incomplete.

In the current issue of Cardiovascular Research, Rucker-Martin et al. [22] have investigated this remodeling feature in human and rat atria, and established that it contributes to alteration of gap junctions as an early event in the development of AF. The authors used several sophisticated imaging techniques (i.e. freeze-fracture EM, TEM and 3D widefield deconvolution microscopy) to study the expression, distribution, and functionality of connexins as well as overall gap junction ultrastructure in human right atrial biopsies obtained from patients in sinus rhythm with dilated atria or in chronic AF, and in rat atria following myocardial infarction with severe structural remodeling but without AF. The authors demonstrated that connexins are redistributed (lateralized) in patients in sinus rhythm with dilated atria, and that similar alterations of connexin expression and gap junction disorganization can be reproduced in an experimental model of atrial myocardial remodeling without AF. Furthermore, regression of the atrial myopathy in rats treated with lisinopril plus spironolactone was shown to be associated with rephosphorylation and polar redistribution of Cx43. These findings suggest that structural remodeling of the atrial myocardium, especially the accompanying fibrosis, is another major factor responsible for gap junction disorganization, and warrant further investigation into the exact relationship between lateral redistribution of connexins and remodeling of the atrial interstitium.

References