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Review article

Exchange of chemical signals between cardiac cells. Fundamental role on cell communication and metabolic cooperation

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ABSTRACT

The exchange of chemical signals between cardiac cells and its relevance for cell communication and metabolic cooperation was reviewed. The role of gap junctions on the transfer of chemical information was discussed as well as the different factors involved in its regulation including changes in cell volume, high glucose, activation of the renin angiotensin aldosterone system including the intracrine effect of renin and angiotensin II on chemical coupling and cardiac energetics. Finally, the possible role of epigenetic changes of the renin angiotensin aldosterone system (RAAS) on the expression of components of the RAAS was discussed. The evidence available leads to the conception of the heart as a metabolic syncytium in which glucose as well nucleotides and hormones can flow from cell-to-cell though gap junctions, providing a new vision of how alterations in metabolic cooperation can induce cardiac diseases. These findings represent a stimulus for future research in this important area of cardiac physiology and pathology.

Contents

1. Gap junctions and electrical coupling

The initial finding that heart cells are isolated by a superficial membrane raised the possibility that the cardiac muscle was not an anatomical syncytium. The development of electronic microscopy, however, made possible to demonstrate that, at the intimate area of cell contact, the cardiac cells are communicated by intercellular channels-the so called gap junctions, which are organized in clusters that span the surface cell membrane of neighboring cells making possible the spread of ions and electrical current from cell-to-cell. The gap junctions consist of connexons forming a central pore and connexin43 (Cx43), which is the main protein in the mammalian heart, has a structure largely conserved among the various isoforms. All connexin proteins consist of 4 transmembrane segments, 2 extracellular loops, 1 intracellular loop and a cytoplasmic amino- and carboxy terminus. Three of these transmembrane segments are mainly hydrophobic amino acids while the third segment shows an amphiphatic character while the two extracellular loops contain three cysteïnes which participate in the process of the two hemichannels docking. The intercellular channel is a weekly selective ion channel permeable

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to hydrophilic molecules up to about 1 kDa molecular weight [1] including (a) a structural apparatus for support; (b) a voltage gate which senses the change in voltage and (c) physical gates within the pore. Studies of molecular permeability limits indicated that the permeability limit of junctional channels is reduced with increasing the molecular weight and negative charge of the molecule [1]. Although previous studies indicated a channel pore of about 16A° observations using atomic force microscopy suggested a larger pore diameter (1.5–2 nm) [71].

Cell-to-cell diffusion of ions and electrical current through gap junctions establishes a "physiological" syncytium what means that the spread of electrical impulse in the cardiac muscle, is dependent not only on the electrical properties of the surface cell membrane but also on the gap junction conductance. Although the classical electrophysiology dedicates a great effort to clarify the types and subtypes and kinetics of ionic channels located at the surface cell membrane, the diffusion of ions and electrical current through the gap junctions is fundamental for electrical and mechanical synchronization in the heart. A decrease of gap junction conductance, for instance, reduces the conduction velocity or even induces a complete blockade of the impulse propagation facilitating the generation of slow conduction and cardiac arrhythmias [2]. During embryonic development these specialized junctions make possible the organization of groups of cells with common phenotypic properties like the cardiomyocytes.

The gap junction conductance is modulated by several factors including second messengers like cAMP and cGMP which changes the junctional conductance through the phosphorylation of junctional proteins [3–5] while intracellular Ca^{2+} which reduces it [6]. Connexin43 (Cx43), which is the most common connexin in the vertebrate heart, is a phosphoprotein [7,8]. Tyrosine phosphorylation of Cx43 decreases the gap junction conductance while protein kinase A (PKA) activation enhances the junctional conductance and permeability [3]. A fall of intracellular pH and phosphorylation elicited by the oncogene v-src [8,9] are also involved in the modulation of junctional conductance in several cell lines but in the vertebrate heart, cell uncoupling elicited by a fall of intracellular pH, is only achieved with extremely low and non physiological levels of pH [9]. Truncation of Cx43, that is, removal of the last 138 amino acids of the terminal tail, makes the channel insensitive to pH or to pp60v-src.

2. Chemical communication between heart cells

The role of gap junctions is not limited to the spread of ions and electrical current from cell-to-cell but involves the intercellular flow of vital metabolites like nucleotides, amino acids, hormones and ATP between cells providing an important mechanism of metabolic cooperation. The cardiac cells have, indeed, all the elements required for receiving and transmitting signals to surroundings myocytes through gap junctions and can be conceptualized as a *metabolic syncytium*. Indeed, evidence has been provided that glucose flows from cell-to-cell through gap junctions in the mammalian heart, indicating that a fall in the intracellular glucose level is sensed by neighboring cells which answer with the delivery of glucose to the depleted cell [10]. The intercellular flow of glucose, which plays an important role as an equalizer of the intracellular glucose concentration and consequent ATP levels throughout the myocardium, has a role on cardiac energetics because when different levels of ATP are present in cardiac cells, an unequal degree of activation of the sodium pump is created generating different intracellular sodium concentrations and discrepant values of membrane potential which impairs the impulse propagation and generates abnormal rhythms. The possible formation of gap junctions, which is known to occurs within seconds, or the increase in junctional permeability, provides an important mechanism of glucose exchange when the ATP levels are depleted.

2.1. Is the formation of gap junctions dictated by metabolic needs?

Cell communication in the heart is a dynamic process. When cardiomyocytes establish contact in tissue culture, gap junction channels are formed within a period of 18 min [50]. In the embryonic heart, the formation of new gap junctions [7] changes the geometry of the heart and exert a fundamental role on the organ form and size. No information is available if gap junctions are formed in the adult heart but during pathological conditions like heart failure, alterations of intracellular calcium, pH and cAMP can alter the junctional permeability with consequent variation of the interchange of metabolites between cells. It is known that cAMP enhances gap junction communication involving not only increase in conductance and permeability but generating new intercellular channels [5]. Perhaps the variation of gap junction permeability is dictated by metabolic needs. According to this view, the depletion of intracellular glucose with consequent decline in the generation of ATP or the disruption of intercellular flow of other compounds like nucleotides, amino acids and peptides through gap junctions, is quickly overcome by the establishment of new intercellular channels or increase in junctional permeability with consequent flow of metabolites between neighboring cells.

Although molecules up to 1 kD can flow easily through the gap junction pores, more recently, evidence has been presented that larger molecules such as peptides and microRNA are able to diffuse through gap junctions [11,12] and that microRNA-133a engineered mesenchymal stem cells, augment cardiac cell survival in the infarct heart [13]. It is then conceivable that the transfer of larger molecules through the junctional channels makes possible not only metabolic cooperation between cardiomyocytes but are involved in heart development and disease as well as in the coordination of gene expression. Indeed, novel findings revealed that miRNAs are important regulators of cellular function during cardiovascular diseases via genetic control [16,53] and that in the adult mouse heart, miR-1 accounts for 40% of total miRNA pool [14] while miR-26 is involved in cardiovascular repair [15]. Furthermore, miR-181 family has anti-inflammatory action [16] and miR-29 seems to be involved in the generation of fibrotic disorders. The arrhythmogenic effects of miR-1 might indicate that miR-1 targets ion channels located at the surface cell membrane and gap junction proteins [see [17]].

2.2. Factors involved in the regulation of chemical communication

2.2.1. Cell volume

It is known that the preservation of normal cell volume is of fundamental importance to cell survival. Variations in cell volume, for instance, activate stretch-sensitive ion channels, changes cell metabolism, gene expression and protein synthesis [26,27]. Furthermore, cell swelling increases the expression of proteins like β-actin, tubulin, cyclooxygenase-2, extracellular signal-regulated kinases ERK-1 and ERK-2, JNK, the transcription factors c-Jun and c-Fos, ornithine decarboxylase, and tissue plasminogen activator [26]. This finding is of particular importance during pathological conditions like myocardial ischemia in which the accumulation of metabolites intracellularly results in cell swelling and consequent activation of stretch-sensitive chloride channel ($ICl_{channel}$) which depolarizes the cell membrane and decreases the action potential duration and refractoriness [28]. Cell swelling also stimulates protein kinase C [26] and enhances tyrosine phosphorylation of several proteins with consequent decline of cell communication [25]. It is known that ion channel proteins may be phosphorylated