Iranian Journal of Pharmaceutical Research (2007) 6 (1): 51-56 Received: March 2006 Accepted: July 2006

Original Article

The Different Mechanisms of Action Potential Propagation in the Heart

Somayeh Mahdavi^{*a*}, Mostafa Rezaei-Tavirani^{*b*}, Farzad Towhidkhah^{*c*}, Shahriar Gharibzadeh^{*d**} and Seyed Hasan Moghaddam niya^{*e*}

^aDepartment of Cellular and Molecular Biology, Khatam University, Tehran, Iran. ^bFaculty of Medicine, Ilam Medical Sciences University; & Asre novin Institute of Research and industrial Services, Tehran, Iran. ^cBiological Systems Modeling Laboratory, Faculty of Biomedical Engineering, Amirkabir University of Technology, Tehran, Iran. ^dNeuromuscular Systems Laboratory, Faculty of Biomedical Engineering, Amirkabir University of Technology, Tehran, Iran. ^eFaculty of Para-medical, Shaheed Beheshti Medical Science University, Tehran, Iran.

Abstract

It was thought previously that cardiac muscle gap junctions provide low-resistance connections between cells and permit the local-circuit current to flow. Some evidences show that myocardial cells may not require low-resistance connections for successful propagation of the action potential (AP). It seems that some other types of mechanisms must be involved in AP propagation.

In this article, we study the different suggested mechanisms of AP propagation. We have calculated different conduction routes and hypothesized novel viewpoints on the mechanisms of conduction in myocyte. It seems that electric field and gap junctions are the main routes for propagation of action potential, but they are affected in different phases of action potential. Gap junction has a dynamic behavior in each cardiac cycle, managing different routes of propagation in the diverse moments. Gap junctions could be open in phases 0, 1, 3 and 4 and close in phase 2 (plateau) of action potential. Whenever gap junction is open, conduction can be fulfilled rapidly by current flow and whenever it is closed, the electrical field will be the main route of propagation.

This view on AP propagation may be useful for better exploitation of drugs or designing new remedies in arrhythmias and diseases that cause diminished cardiac contractility such as cardiac failure.

Keywords: Action potential propagation; Potassium concentration; Sodium concentration; Gap junction.

Introduction

Gap junctions are specialized structures in the plasma membrane of two adjacent myocytes. Protein oligomers of gap junctions are located along each other in neighboring cells, forming conduits for intercellular communication that allow exchange of nutrients, metabolites, ions, and small molecules up to 1,000 Da (1, 2).

It was not long ago that cardiac muscle was generally thought to be a smoothly conducting tissue whose cells were extensively interconnected to neighbors, effectively

^{*} Corresponding author:

E-mail: gharibzadeh@aut.ac.ir

Mahdavi S, Rezaei-Tavirani M, Towhidkhah F, Gharibzadeh S and Moghaddam niya SH / IJPR 2007 6, (1): 43-50

providing low-resistance connections to all neighboring cells and free flow of local-circuit current (3-5). We now know that these are not completely correct (6, 7).

One of the first hints is that the ventricular myocardial cells of some vertebrate hearts may not be connected by low-resistance pathways (8). It has also been proposed that myocardial cells may not require low-resistance connections for successful propagation of the Action potential (AP) (9, 10) and a similar proposal was made for smooth muscles (11). Furthermore, the gap junctions may close under certain conditions (e.g. acidosis, high [Ca]i etc.) (2, 12-14).

Therefore, it seems that some other types of mechanisms must be involved in AP propagation (4). In this article, we study the different suggested mechanisms and their importance in propagation of action potential.

Experimental

Methods

In this study, we use the other researches in order to analyze the present opinions and hypothesize novel viewpoints on the mechanisms of conduction in cardiac cells. Whenever possible, we have exploited calculation to determine relative significance of each route and compared them with each other.



Figure 1. Different routes of conduction in cardiac tissue. A) gap junction B) electric field C) potassium accumulation D) sodium accumulation.

Analysis of transmission mechanisms during excitation

Different mechanisms have been suggested for propagation of action potential in cardiac tissue:

1- Gap junction, 2- Potassium accumulation,

- 3- Sodium accumulation, 4- Electric field (EF),
- 5- Calcium current, 6- Capacitive coupling.

Gap junction

The electromicroscopic and electrophysiological results show the presence of low resistance pathway interconnecting the cardiac myocytes, functioning as a fundamental route for impulse transmission (3). Gap junctions provide a conduit for passage of molecules and ions. Hence, local-circuit current can pass from one cell to the next. This route of transmission is called electrical coupling (4). In this view, gap junction channels are major determinants of intercellular resistance to current flow (5).

Several evidences show that gap junction is necessary for transmission of excitation. However, experimental studies on mice lacking gap junctions, demonstrated abnormality in AP propagation (15, 16). In addition, some simulations confirm this role for gap junctions (17).

Potassium accumulation

During excitation, the electrochemical driving force for net outward K^+ current increases in proportion to depolarization. Therefore, efflux of K^+ across all surfaces of the cell will suddenly increase during the rising phase of the AP, even if K^+ conductance (gk) remains constant. However, some researchers believe that the K^+ flux into the narrow junctional cleft will accumulate and depolarize the post-Junctional membrane (4).

Calculation of the effect of pre-junctional cell action potential on the interjectional potassium accumulation is as follows:

The junction is like a cylinder, 4 nm long (1) and 16 um in diameter (18). Therefore, the volume of junction is:

$$R=8\times10^{-6} m$$
 (1)

$$L = 1 \times 10^{-9} m$$
 (2)

$$V = L\pi r^2$$
(3)

The junction volume is:

$$V=3.14\times(8\times8\times10^{-12})\times10\times10^{-9}=2\times10^{-18}m^{3}$$
(4)

In each action potential, 6000 ions transfer through each membrane square micrometer (19). Therefore, the amount of transferring ions through junction in one action potential is:

$$A = \pi r^{2}$$
(5)

$$A=3.14\times(8\times8\times10^{-12})=2\times10^{-10} \text{ m}^2$$
 (6)

The total number of ions in the junction is: $(6000 \times 200 \times 10^{-12})/10^{-12} = 1200000$ ion (7)

And the number of moles in the gap is:
$$(1.2 \times 10^6)/(6.02 \times 1023)=2 \times 10^{-18}$$
 mole (8)

This ion molarity change can alter the cleft potential as bellow:

$$(2 \times 10^{-18})/(2 \times 10^{-15}) = 1 \text{ mmol/l}$$
 (10)

Then:

$$\frac{E1}{E2} = \frac{\log[K]o1 \cdot \log[K]i1}{\log[K]o2 \cdot \log[K]i2} = 1.06\text{mv} \quad (11)$$

and the new voltage will be:

774

$$E2 = \frac{E1}{1.06} = \frac{907}{1.06} = -84 \text{ mv}$$
(12)

Hence, the theoretical analysis shows that the change caused by K^+ accumulation is not considerable.

Sodium accumulation

Some researchers believe that this mechanism, against to the potassium accumulation causes sodium current into the prejunctonal membrane and develops a negative potential in the narrow junctional gap and leads to electrical transmission between contiguous excitable cells, without any need to direct electrical current through gap junctions (4, 20).

According to formulas 1 to 10, change of sodium accumulation in a cleft during one action potential is 1 mmol/l. It is obvious that this change is in the reverse direction of potassium. Therefore, the cleft potential is altered as bellow:

$$\frac{E1}{E2} = \frac{\log[Na]o1 \cdot \log[Na]i1}{\log[Na]o2 \cdot \log[Na]i2} = 1.01$$
(13)

So, the new voltage will be:

 L^{1}

$$E2 = \frac{E1}{1.01} = -89 \text{ mv} \tag{14}$$

This change of sodium accumulation can cause a negative potential in the junction but as it is obvious, this is not sufficient to depolarize the post junctional cell.

Electric field

Another possible mechanism for the interaction between closely abutting excitable cells is by the EF that develops in the narrow junctional cleft between the cells during excitation of the pre-JM (10). The EF model only requires that the pre-JM and post-JM be excitable membranes having a slightly lower threshold than the surface sarcolemma (perhaps resulting from an increased density of fast Na⁺ channels). The electrical potential that develops in the narrow junctional cleft between cells during excitation of the pre-JM acts to depolarize the post-JM to threshold by diminishing the voltage gradient across it (4, 21). Sperelakis has presented models, indicating that in the lack of gap junctions, electric field is sufficient for action potential propagation (4, 18).

Calcium current

Some evidences show that in some situations, electrotonic calcium conduction is responsible for propagation of action potential (22, 23).

The study of Shaw and Rudy, claiming that electrotonic calcium current sustains conduction whenever intercellular coupling is reduced, is somehow consistent with this mechanism (22).

Capacitive coupling

It seems that capacitive coupling is involved partly in transmission. However, it has been noted that the capacitance of cells are less than what is needed to produce a prominent conduction (18). Mahdavi S, Rezaei-Tavirani M, Towhidkhah F, Gharibzadeh S and Moghaddam niya SH / IJPR 2007 6, (1): 43-50

Results and Discussion

None of these mechanisms can exactly be sufficient for propagation of action potential. While most of studies show that gap junctions are necessary for propagation of action potential, some other evidence demonstrates the reverse results. Sperelakis model shows that addition of few gap junction channel causes propagation velocity to become greatly increased and out of the physiological range. Therefore, he proposed that in those cases and (or) species in which gap junctions are present, most of the gap junction channels may be closed during propagation (24, 25). Some other experimental evidences also show that the number of available gap junctions is much larger than needed for the propagation of action potential in normoxic condition (13).

On the other hand, the propagation of action potential is normally discontinuous (26), but the ordinary number of gap junctions cannot create this state (24, 25).

Also the different documents disprove the mechanism of potassium accumulation as below:

-There is no evidence to approve that the concentration of potassium in junctional cleft is more than other parts of cardiac tissue.

-The increase of potassium accumulation in each cardiac cycle is very little and it is not sufficient to change the post junctional membrane potential to threshold. Our calculations show that it can change the junctional cleft potential only about 0.09 mv.

-Moreover, this altered potassium concentration diffuses in the bulk interstitial fluid and approaches to the normal value, damping the voltage change.

-The activity of Na, K-ATPase retunes the additional junctional potassium into the cells

-In the same time, the effect of sodium concentration is reverse and it can counteract the effect of potassium accumulation.

By the same reasons, changes in sodium accumulation are too little to propagate the action potential.

Moreover, different evidences against electric field, mainly proposed by Sperelakis, are as follow:

Several experiments on mice with lacking

gap junctions show abnormality in AP propagation (5, 6). Alteration of gap junction organization and connexin expression are now well established as a consistent feature of human heart disease in which there is an arrhythmic tendency (27-29). Acute myocardial ischemia is the major cause of cardiac death, related to gap junction uncoupling and abnormality (13). These evidences suggest the importance of gap junction in AP propagation.

It is worth noting that although the changes of sodium, potassium and calcium during action potential are little, but they can facilitate the AP propagation as the accessory route. For example in conditions that gap junction can not work truly these mechanisms may become considerable (20, 22).

There are no definite documents to accept or deny each mechanism absolutely. It seems that action potential is propagated by the combination of different mechanisms (3, 4).

As we previously proposed, the both main mechanisms (gap junction and electric field) are necessary for normal cardiac functioning; but in different times of a cardiac cycle. We think that gap junctions are not continuously open in a normal heart cycle; instead, they open and close intermittently. Consequently, whenever gap junction is open, conduction can be fulfilled rapidly by current flow and whenever it is closed, direct current cannot transfer rapidly and the electrical field will be the main route of propagation.

It seems that gap junction has a dynamic behavior in each cardiac cycle, managing different routes of propagation in the diverse moments of normal cycle.

The understanding of AP propagation may be useful for better exploitation of drugs or designing new remedies in arrhythmias. For instance, drugs that can open the gap junctions in hyperpolarized state and close them in depolarization, seem to be more useful in treating arrhythmias. In addition, the introduction of drugs, which can open the gap junctions when intracellular calcium concentration is low and close them when it is high are recommended.

On the other hand, paying attention to dynamic behavior of gap junction can be useful in treating the diseases that cause diminished cardiac contractility such as cardiac failure. Since the closure of gap junctions in phase 2 of AP leads to increased calcium concentration, we hypothesize that gap junction closing drugs may be effective in such conditions (30).

An advantage of studying the aforementioned mechanisms of action potential propagation is the ability to interpret some heart arrhythmia mechanism. It is mentioned in previous studies that potassium is related with different arrhythmias, so that its decrease increases the cell excitability, and its increase, raises the action potential duration. However, no body has paid attention to the effect of this increment on the excitation of the cell. Based on our calculations, abnormal increase of potassium may produce ectopic excitation.

It must be noted that although hypotheses and model studies are important tools to catch the truth about diseases and their treatments, but surely empirical and clinical studies are needed to find the definite solution for cardiac disorders.

References

- Yeager M. Related Structure of cardiac gap junction intercellular channels. J. Struct. Biol. (1998) 121: 2312-2345
- (2) Spray DC and Burt JM. Structure-activity relations of the cardiac gap junction channel. Am. J. Physiol. (1990) 258: C195-220
- (3) Rohr S. Role of gap junctions in the propagation of the cardiac action potential. *Cardiovasc. Res.* (2004) 62: 309-322
- (4) Sperelakis N and McConnell K. Electric field interactions between closely abutting excitable cells. *IEEE Eng. Med. Biol. Mag.* (2002) 21: 77-89
- (5) Davis LM, Rodefeld ME, Green K, Beyer EC and Saffitz JE. Gap junction protein phenotypes of the human heart and conduction system. J. Cardiovasc. Electrophysiol. (1995) 6: 813-822
- (6) Sperelakis N. Electrical field model for electric interactions between myocardial cells. In: Sideman S and Beyar R. (eds.) *Electromechanical Activation*, *Metabolism, and Perfusion of the Heart Simulation and Experimental Models*. The Hague: Martinus Nijhoff (1987) 77-113
- (7) Sperelakis N and McConnell K. An electric field mechanism for transmission of excitation from cell to cell in cardiac muscles and smooth muscles. In: Mohan RM. (ed.) *Research Advances in Biomedical Engineering*. Vol. 2, Trivandrum, India (2002) 39-66
- (8) Sperelakis N, Hoshiko T, Keller RF Berne RM. Intracellular and external recordings from frog

ventricular fibers during hypertonic perfusion. Am. J. Physiol. (1959) 198: 135-140

- (9) Sperelakis N. Lack of electrical coupling between contiguous myocardial cells in vertebrate hearts. In: McCann FV. (ed.) Comparative Physiology of the Heart: Current Trends. Birkhauser Verlag, Basel (1969) 135-165
- (10) Picone JB, Sperelakis N, Mann JE Jr: Expanded model of the electric field Hypothesis for propagationn in cardiac muscle. Math and computer modeling 1991, 15: 17-35
- (11) Daniel EE, Daniel VP, Duchon G, Garfield RE, Nichols M, Malhotra SK and Oki M. Is the nexus necessary for cell-to-cell coupling of smooth muscle? *J. Membr. Biol.* (1976) 28: 207-239
- (12) Beardslee MA, Lerner DL, Tadros PN, Laing JG, Beyer EC, Yamada KA, Kleber AG, Schuessler RB and Saffitz JE. Dephosphorylation and intracellular redistribution of ventricular connexin 43 during electrical uncoupling induced by ischemia. Circ Res. 2000 Oct 13,87(8): 656-62
- (13) De Groot JR and Coronel R. Acute ischemia-induced gap junctional uncoupling and arrhythmogenesis. *Cardiovasc. Res.* (2004) 62: 323-334
- (14) Ruiz-Meana M, Garcia-Dorado D, Lane S, Pina P, Inserte J, Mirabet M and Soler-Soler J. Persistence of gap junction communication during myocardial ischemia. Am. J. Physiol. Heart Circ. Physiol. (2001) 280: H2563-2571
- (15) Verheule S, van Batenburg CA, Coenjaerts FE, Kirchhoff S, Willecke K and Jongsma HJ. Cardiac conduction abnormalities in mice lacking the gap junction protein connexin40. J. Cardiovasc. Electrophysiol. (1999) 10: 1380-1389
- (16) Simon AM, Goodenough DA and Paul DL. Mice lacking connexin40 have cardiac conduction abnormalities characteristic of atrioventricular block and bundle branch block. *Curr Biol.* (1998) 8: 295-298
- (17) Rudy Y and Quan WL. A model study of the effects of the discrete cellular structure on electrical propagation in cardiac tissue. *Circ. Res.* (1987) 61: 815-823
- (18) Sperelakis N and Ramasamy L. Modeling electric field transfer of excitation at cell junctions. *IEEE Eng. Med. Biol. Mag.* (2002) 21: 130-143
- (19) Alberts B, Johnson A, Lewis J, Raff M, Roberts K and Walter P, *Molecular Biology of the Cell*. 4th ed. Galand Science, New York (2002) 675-800
- (20) Kucera JP, Rohr S and Rudy Y. Localization of sodium channels in intercalated disks modulate cardiac conduction. *Circ. Res.* (2002) 91: 1176-1182
- (21) Sperelakis N and Mann JE. Evaluation of electric field changes in the cleft between excitable cells. *J. Theor. Biol.* (1977) 64: 71-96
- (22) Shaw RM and Rudy Y. Ionic mechanisms of propagation in cardiac tissue. Roles of the sodium and L-type calcium currents during reduced excitability and decreased gap junction coupling. *Circ. Res.* (1997) 81: 727-241
- (23) Shaw RM, Rudy Y. Electrophysiological effects of

acute myocardial ischemia. A mechanistic investigation of action potential conduction and conduction failure. *Circ. Res.* 1997 Jan, 80(1): 124-138

- (24) Sperelakis N. Propagation of action potentials between parallel chains of cardiac muscle cells in PSpice simulation. *Can. J. Physiol. Pharmacol.* (2003)81:48-58
- (25) Sperelakis N. Combined electric field and gap junctions on propagation of action potentials in cardiac muscle and smooth muscle in PSpice simulation. J. Electrocardiol. (2003) 36: 279-293
- (26) Delgado C, Steinhaus B, Delmar M, Chialvo DR and Jalife J. Directional differences in excitability and margin of safety for propagation in sheep ventricular epicardial muscle. *Circ. Res.* (1990) 67: 97-110
- (27) Severs NJ, Coppen SR, Dupont E, Yeh HI, Ko YS and Matsushita T. Gap junction alterations in human cardiac disease. *Cardiovasc. Res.* (2004) 62: 368-377
- (28) Severs NJ, Cardiovascular disease. *Novartis Found Symp.* (1999) 219: 188-206
- (29) Jongsma HJ and Wilders R. Gap junctions in cardiovascular disease. *Circ. Res.* (2000) 86: 1193-1197
- (30) Mahdavi S, Rezaei-Tavirani M, Gharibzade S and Towhidkhah F. Dynamic behavior of gap junctions in each cardiac cycle: A novel view on the electrical coupling of normal cadiocytes. *Medical Hypotheses*, accepted for publication.

This article is available online at http://www.ijpr-online.com