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Review article

EVOLUTION OF AUTOMATICITY OF HEART PACEMAKER STUDIED FROM A THEORETICAL PERSPECTIVE

Vijay Kumar Konuri[1], Mohammed Abdul Hannan Hazari[2], Ravi Kumar K[3], Chandrasekhar M[4], Ambareesha K[5], Ram Reddy B[6]

[1]Associate Professor, Department of Anatomy, All India Institute of Medical Sciences, Raipur, Chhattisgarh, India
[2]Associate Professor, Department of Physiology, Deccan College of Medical Sciences, Kanchanbagh, Hyderabad, Telangana, India
[3]Assistant Professor of Anatomy, Govt Medical College, Jagdalpur, Chhattisgarh
[4]Professor and HOD, [5]Tutor, Department of Physiology, Meenakshi Medical College, Kanchipuram, Tamil Nadu
[6]Professor & HOD, Department of Physiology, Apollo Institute of Medical Sciences and Research, Jubilee Hills, Hyderabad, Telangana, India.

*Corresponding author email**:** vkkonuri@gmail.com

ABSTRACT

The pacemaker of the mammalian heart had developed a robust and yet a flexible system in the course of evolution whose function is based on multiple interactions at the sub-cellular, cellular and finally at the tissue level. These, in turn, should respond to extrinsic signals. Cardiac action potentials were explained for a long time based on the changes that occur at the cell surface. New hypothesis was put forward at the turn of the century that pointed to the role of intracellular calcium clock. Discovery of ryanodine receptors, fluorescence labeling techniques, confocal imaging and finally computer modeling of physiological processes had brought about a noticeable change that allowed development of a new concept of pacemaker automaticity. Reviewing all these developments we hereby put forward a few theoretical formulations that can turn out to be new instruments in advancing our knowledge of cardiac physiology. We had theorized that cardiac muscle is an emergent property of smooth muscle in the course of evolution, and that pacemaker activity of the cardiac muscle underwent a phase transition that finally led to the evolution of a structural pacemaker.

Keywords: Heart, Pacemaker, Automaticity, Evolution

INTRODUCTION

The sino-atrial node (SAN) pacemaker cells produce billions of incessant and uninterrupted beats in the course of the life time of an individual. It is evident that the pacemaker of the mammalian heart has developed a robust and yet a flexible system in the course of evolution [1]. Robustness indicates the fail-safe properties and flexibility signifies the adaptability to changes in the demands made on it. The pacemaker function is based on multiple interactions at the level of sub-cellular, cellular and finally at the level of tissue architecture, which in turn should react to extrinsic signals like stretch, electrical and chemical signals that act on the cell surface receptors.

The generation of action potentials in the myocardium was explained for a long time, predominantly, basing on the changes that occur on the cell surface and its ion channels [2]. However, the

turn of the century has brought new evidence pointing to the role of an intracellular clock. This turned out to be the cyclical rhythm of cytosolic Ca^{2+} concentration. Sarcoplasmic reticulum (SR) has proved to be having the capacity to operate another physiologic clock of calcium cycles[3]. Recent developments in experimentation like confocal imaging have revealed the presence of multiple spontaneous, rhythmic, local calcium releases[4]. These tightly regulated processes begin to occur beneath the cell surface during the later part of diastolic depolarization. This activates the Na^+-Ca^{2+} exchanger that causes an explosive increase in diastolic depolarization and leads to the activation of L-type calcium channels[5].

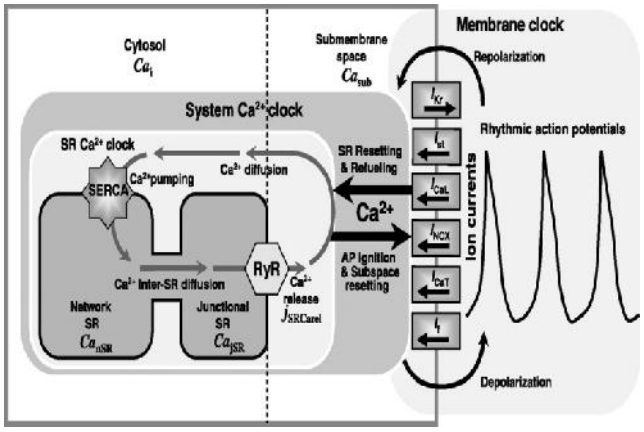

Fig 1. Interplay between intracellular and membrane surface Ca^{2+} clock.

The existing understanding of cardiac action potentials

The explanation of action potentials in the working myocardium is as follows. Phase 0 or the rapid depolarization results from the opening of the fast Na^+ channels. Phase 1 of the action potential starts the repolarization process and is attributed to the closing of Na^+ channels and inward movement of Cl^- ions. Phase 2, the so-called "plateau" phase of the action potential results from several mechanisms but could be mainly because of slow inward movement of Ca^{2+} and Na^+. Phase 3 involves relative rapid repolarization, commencing with inactivation of slow Ca^{2+} and Na^+ channels and rapid outward movement of K^+ ions. Phase 4 restores the ionic composition back to the resting state by Na^+-K^+ ATPase which pump Na^+ ions out and K^+ ions inside the cell[6].

Membrane potential of pacemaker cells spontaneously declines to the firing level and is known as prepotential or pacemaker potential which triggers the next action potential. At the peak of each action potential, conductance of potassium (IK^+) begins and repolarization occurs. IK^+ then declines and the membrane potential reaches slight hyperpolarization. At this instance an "h" or "f" channel which allows both Na^+ and K^+ is activated. As conductance through "h" channel (Ih) increases, the membrane begins to depolarize forming the initial part of the prepotential. T-type Ca^{2+} channels then open and its conductance ($ICa^{2+}{}_T$) completes the prepotential. At this juncture L-type Ca^{2+} channels open and $ICa^{2+}{}_L$ produce action potential.

The measurements of calcium concentrations

The finding that oscillations in Ca^{2+} concentrations were inhibited by calcium channel blockers (CCBs) had brought to the fore the idea that Ca^{2+} concentration represents a two-way interaction between the intracellular Ca^{2+} stores and the membrane surface potential changes[7]. But due to the rapidity of changes; spontaneous, localized oscillations of the calcium clock could not be measured within the individual SA nodal cells and hence the concept that initiators of the normal automaticity of pacemaker cells are internal calcium oscillations could not be established.

The membrane surface processes was disconnected from that of intracellular oscillations, for a long time, by the employment of Ca^{2+} overload conditions to voltage clamp studies[8]. Studies have gradually demonstrated that the intracellular oscillations could, in fact, produce spontaneous membrane currents. It is now considered that the intracellular oscillations involve the cycling of Ca^{2+} ions between SR and cytosol[9].

Discovery of ryanodine receptors

Then came the discovery that the drug named ryanodine can have a profound negative chronotropic effect on the automaticity of cardiac pacemaker cells. By studying the effect of ryanodine on the contour of the action potential it was suggested that Ca^{2+} released from the SR contributes to diastolic depolarization[10].

It is now possible to measure the intracellular calcium levels in spontaneously firing pacemaker cells of SAN which made it clear that each spontaneous action potential evokes a calcium gradient in the cytosol and that the influx of calcium through L-type calcium channels affects the calcium loading of the

SR. Intracellular buffering of calcium has the potency to block the generation of spontaneous action potentials[11]. This constitutes a strong evidence in favor of the idea that normal automaticity of pacemaker cells is strongly linked with the dynamics of intracellular calcium.

Modern techniques

Fluorescence imaging of intracellular calcium is made possible in the last decade that enabled to document not only the global transients of cytosolic calcium but also of many localized calcium releases beneath the cell surface during late diastolic depolarization[12]. Such local calcium releases are observed in SA nodal cells in the absence of changes in the membrane potentials, i.e. in voltage clamped SA node pacemaker cells. There is evidence that local Ca^{2+} release from the sarcoplasmic reticulation (Ca^{2+} sparks) occurs during the prepotential. Local calcium releases (LCRs) during the late diastolic depolarization begin to boil and then explode into an action potential[13].

A tiny change in the current to the degree of 3 pA is enough to explode into an action potential during the critical diastolic depolarization phase of rabbit SA node cells. Although the individual local release of calcium during the diastolic depolarization of pacemaker cells is relatively small and stochastic in nature, the synchronized and cumulative effects of LCRs imparts and impacts the rising phase of diastolic depolarization leading to the next action potential. A failure to generate an exponential phase in diastolic depolarization is the consequence of a failure to generate diastolic INCX[14].

Structurally SA node is heterogeneous

Till now we discussed the mechanisms of automaticity and spontaneous calcium cycles in individual pacemaker cells. But cardiac pacemaker function cannot be understood completely by the study of the intrinsic properties of the pacemaker cells. Advanced histological studies had revealed that SA node is a highly heterogeneous structure with small pacemaker cells predominantly located in the centre[15]. The SA nodal tissue is characterized by complex cell-to-cell interactions in generating the highly robust impulses with a fail-safe mechanism[16]. The function of the pacemaker tissue within the SA node is determined by the intrinsic properties of individual cells that are being modulated by several factors of the local environment within the SA node[17]. The pacemaker tissue is at the same time being influenced by extrinsic modulators that include the electrical and mechanical forces as well as the autonomic milieu. These modulatory factors are heterogeneous throughout the SA node which could explain the differences in the shape of the action potential curves of different cells in the same locality[18]. This could be the result of mutual interaction between the depolarizing charges generated by individual SA node cells and the structural properties of the surrounding non-excitable tissue[19].

Extensive amounts of connective tissue and numerous fibroblasts occupy from 25% to almost 90% of the area of SA node[20].

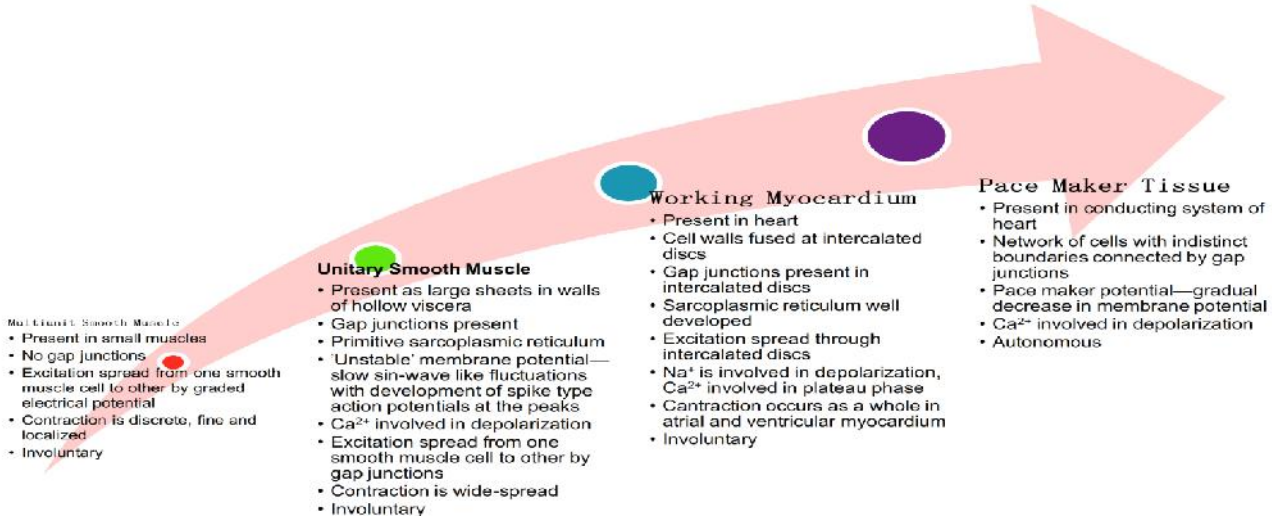

Fig 2: Phase transition and emergence of cardiac muscle from smooth muscle with maintenance of legacy in some aspects

In addition to bands of connective tissue, the gap junction proteins are also found to be located in various types and with varying densities in near vicinities. The myofilament density decreases from periphery to the centre of the SA node[21]. The nerve endings and autonomic receptors on pacemaker cells are found to be at the highest density in the central area of SA node[22]. All these structural features make the SA node a highly heterogeneous structure that can generate not only flexible but also a robust action potential[23].Intracellular calcium cycling plays a major role in the generation of automaticity in embryonic cardio myocytes and so could be used to generate stem cell derived spontaneously beating myoblast cells[24].

Discussion: A theoretical approach is needed to interpret physiology at an advanced level

We have seen how our concepts of pacemaker potentials transformed over time, from the more or less simplified notions that membrane currents explain everything to developing a more and more complex picture of mutual entrainment of the cytosolic and the membrane clocks and of their different mechanisms in generating automaticity.

We understand the vertebrate circulatory system as a closed canal system comprised of network of smooth muscle and other cells, the proximal part of which has been transformed into cardiac muscle due to increased circulatory load imposed on the system[25].This can be visualized as a type of phase transition during evolution of smooth muscle there by transforming phase maker activity from a network of molecules to a network of cells and tissues, which can justify the existence of special conducting system in myocardium. So this can be generalized as an emergent property of smooth muscle. Pacemaker properties of the smooth muscle is well preserved but is now regulated by pacemaker system of cardiac muscle. Even in smooth muscle the initiation of pacemaker activity is due to the oscillations of intracellular calcium that are being modulated by external conditions. It is our endeavor to elucidate how function is translated into structure through the alteration of the genetic program.

CONCLUSION

Pacemaker in mammalian heart is the phase shift transformation of the smooth muscle through cardiac muscle during the evolutionary process. In the course of development of highly evolved forms of organisms, the metabolic necessities of the complex tissues and organs demanded continuous supply of nutrients and gases for sustenance of life. Hence, the smooth muscle underwent structural and functional adaptations to develop into cardiac muscle which further acquired autonomy at the expense of losing the contractility to form pacemaker tissue. This aptly describes the proverb *"Necessity is the mother of invention"*.

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