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The Central Brain of the Heart:

The Sinoatrial Node

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Spontaneous action potentials generated by the pacemaker cells of the sinoatrial node (SA) node are the first step in the chain of events that comprise each cardiac cycle. Despite the apparent lack of cellular organization and a high degree of functional heterogeneity[1–4] in the SA node compared to the rest of the heart, it is remarkable that it can generate highly periodic, rhythmic depolarizations that are rapidly transmitted throughout the working myocardium with high fidelity.

To generate a heartbeat with enough force to push blood throughout the systemic and pulmonary circulations, action potentials originating in the SA node are conducted throughout the atria first, after which they pass through the atrioventricular node, reaching the Purkinje fibers and then the right and left ventricles. Electrical connectivity via gap junctions between pacemaker and transitional cells mediates the transmission of impulses out of the SA node during each cardiac cycle. Action potentials generated in the SA node can occur without extrinsic autonomic input, suggesting that intrinsic control and regulation is sufficient for action potential generation and propagation.

To communicate effectively with one another and the surrounding myocardium, SA node pacemaker and nonpacemaker cells must be either directly electrically coupled or rely upon other mediators to aid in this effort. Nonpacemaker cell types in the SA node are considered suitable candidates for mediating and integrating the electrical activity of pacemaker cell populations across the SA node.

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For decades, the generally accepted conceptual model of pacemaking activity was based on an entrainment mechanism (recently reviewed by Guarina et al[5]). In this model, action potentials are generated by clusters of pacemaker cells firing in unison and propagate via gap junctions to neighboring SA node myocytes and, eventually, to surrounding atrial myocytes. SA node myocytes that fire action potentials at the highest frequency become the dominant (leading) pacemaker site. Accordingly, the entrainment model predicts that functional heterogeneity dissipates as the cells become synchronized.

Recent work by Grainger et al,[2] Clancy and Santana,[6] and Bychkov et al[7] challenged this long-held view, proposing an alternative conceptual model in which periodic pacemaking activity by the SA node does not simply result from dissipation of electrical heterogeneity, as proposed by the entrainment model, but rather is caused by electrical heterogeneity, potentially via a stochastic resonance mechanism similar to the one proposed for neural circuits.

In this issue of *JACC: Clinical Electrophysiology*, Bychkov et al[8] investigate the relationship between pacemaker and nonpacemaker cell types in the SA node using high spatial resolution imaging approaches. The investigators also discuss the parallels between their findings on the organization of multiple cell types in the SA node and how this correlates to brain cytoarchitecture. Indeed, they suggest that SA node structural organization promotes interactions between heterogeneous cell types to achieve synchronized impulse generation.

The investigators elegantly apply detailed immunolabeling methods coupled with confocal and transmission electron microscopy to carefully map the ultrastructure of the pacemaker functional unit. Ultimately, this complex level of multicellular interaction promotes the generation of the normal heartbeat and ensures adequate rhythm. Bychkov et al[8] propose a novel mechanism for pacemaker cells to communicate on an intercellular level through the formation of functional units composed of SA node pacemaker cells, autonomic ganglia, telocytes, and peripheral glial cells. The investigators also examine the functional significance of telocytes that express the Ca^{2+}-binding protein, S100 calcium-binding protein B (S100B). They perform imaging of Ca^{2+} signals in HCN4-GCaMP8–expressing mice and microelectrode recordings of action potentials to support a role for S100B in disrupting SA node pacemaker cell Ca^{2+} signaling synchronicity and impulse properties.

In a previous study by the same group, Bychkov et al[7] determined that electrical impulses emerge from heterogeneous local Ca^{2+} signaling both within and among cells of pacemaker tissues. This heterogeneity in electrical signaling is consistent with the work by Grainger et al,[2] who found that the organization of the SA node microvasculature varies regionally, a variability that serves to match blood supply to local myocyte excitability. The highly vascularized superior SA node is populated by myocytes capable of undergoing periodic voltage oscillations. By contrast, inferior SA node myocytes have a low action potential firing rate and are sparsely vascularized.

The recent study by Bychkov et al[7] challenges the long-held view that a dominant or master pacemaker is responsible for controlling all other pacemakers, and instead, suggests a system of coupled oscillators that display diverse subthreshold Ca^{2+} signals and full-scale

action potentials. The investigators reasoned that like the brain and its many neurons, the SA node must possess the ability to integrate the multitude of behaviors across the pacemaker cell network to produce an action potential and propose that the SA node is “neuromimetic.” This neuromimetic microenvironment that is created by telocytes, and glial and neuronal interactions that surround pacemaker cells is likely dedicated to regulating localized Ca^{2+} release events from the sarcoplasmic reticulum within individual pacemaker cells, but also the regulation of intercellular communication among pacemaker cells that ultimately impacts heart rhythm.

The current study also suggests further parallels between the SA node and brain. Fascinatingly, projections from SA node peripheral glial cells made close associations with SA node vasculature, suggesting that like the brain, glial-vascular associations may be important for “cardio-vascular coupling,” providing a means to regulate microvascular blood flow in response to changes in pacemaker activity, reminiscent of astrocytic end-feet making the connection between neurons and cerebral vasculature that mediate neurovascular coupling. Other groups have similarly drawn comparisons between the SA node and brain. A report by Hennis et al[9] suggest that nonfiring pacemaker cells in the SA node are physiologically important and provide stabilization of the SA node network to promote normal function by inhibiting overshooting excitation. They propose that this is like the role that interneurons play in ensuring balance in neural brain networks.

In this current study, our improved understanding of the distribution and role of telocytes and peripheral glial cell types in the SA node opens the opportunity to further dissect their function. Whereas telocytes have been observed in other organs (eg, gastrointestinal tract, uterus, and pancreas), SAN telocytes have been relatively understudied. A recent report by Mitrofanova et al[10] characterized telocyte expression in the human SAN and postulated that telocytes may act as mediators of cellular communication between pacemaker cells and the working myocardium, underscoring their clinical importance.

To our knowledge, the present study by Bychkov et al[8] is the first to investigate the effects of S100B on Ca^{2+} dynamics and action potential generation in the SA node. It will be important to understand whether S100B is modulating the Ca^{2+} or membrane clocks, and if so, it will be critical to determine a potential role for this mechanism in arrhythmogenesis. Although this study thoroughly characterizes the anatomical location of multiple cell types in the SAN, the investigators do not provide accurate quantification of cellular density. Such measures will be essential to distinguish, for example, whether sex-dependent cellular density differences exist and to identify subtle regional expression differences, particularly between the superior and inferior SA nodes. Recent work by Brennan et al[3] and others[2] are beginning to appreciate the heterogeneity between the superior SA node and inferior SA node that have roles in disease (ie, heart failure). While adding to the expanding complexity of the SA node, the findings by Bychkov et al[8] provide another layer of regulation that offers a means to organize the seemingly chaotic heterogeneity to generate organized, rhythmic action potentials.

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