The Sinoatrial Node Is Still Setting the Pace 100 Years After its Discovery

M.R. Boyett, H. Dobrzynski

The mammalian sinoatrial node, the pacemaker of the heart, was discovered 100 years ago in the countryside of Kent (UK) in “a cosy, squat, red-roofed farmhouse, embowered in creepers, separated from the road by a richly stocked garden” with “a horse going round and round winding up a huge bucket from a very deep well” and a “farmyard, filled with healthy farmyard manure.” Arthur Keith (later Sir Arthur) had converted the drawing room into a laboratory and recruited the assistance of Martin Flack, the son of the local butcher and grocer and a young medical student at the time. One evening when Keith and his wife, Celia, returned from a bicycle ride, Flack showed him a “wonderful structure” he had discovered in the heart of a mole (perhaps caught on the farm?)—so was discovered the “wonderful structure” he had discovered in the heart of a mole (perhaps caught on the farm?)—so was discovered the sinoatrial node. Keith and Flack published the discovery of the sinoatrial node in 1907 in the Journal of Anatomy and Physiology. Curiously, only a few years later, Keith was to become embroiled in one of the biggest scientific scandals of all time, ‘Piltdown man’, a fraudulent ‘missing link’. Now 100 years after the discovery of the sinoatrial node, we are still making new discoveries about the workings of the sinoatrial node as shown by the paper from Ju and Allen and colleagues in this issue of Circulation Research—the sinoatrial node is still setting the pace!

In the 1970s and 1980s a flurry of voltage clamp studies, first on multicellular preparations of sinoatrial node tissue and then on isolated sinoatrial node cells, appeared to establish the mechanism of pacemaking in the sinoatrial node. At this time, pacemaking was primarily thought to be result of the decay of delayed rectifier K⁺ current (K⁺ current decay hypothesis) together with the activation of various inward currents (funny current and T- and L-type Ca²⁺ currents) and facilitated by an elusive inward background current and the lack of inward rectifier K⁺ current. At the same time, it was known that in Ca²⁺-overloaded Purkinje fibers or ventricular muscle, spontaneous Ca²⁺ release could occur from the sarcoplasmic reticulum (SR). By activating inward Na⁺-Ca²⁺ exchange current, this could produce “TDs” or transient depolarizations, which in turn could result in abnormal pacemaker activity; this abnormal pacemaker activity (resulting from an “internal oscillator”) was thought to be distinct from sinoatrial node pacemaker activity (resulting from a “surface membrane oscillator”). Ju and Allen were among the first to raise the possibility that SR Ca²⁺ release together with Na⁺-Ca²⁺ exchange could be involved in normal pacemaking in the heart. Ju and Allen worked on the sinus venosus of the toad, while Terrar and Lakatta and colleagues extended the concept to the mammalian sinoatrial node. Although all investigators agree that intracellular Ca²⁺ is involved in pacemaking, there is controversy concerning the degree of its importance. Our view is that many factors are involved in pacemaking, for example rapid and slow delayed rectifier K⁺ currents, funny current, cardiac and neuronal-type Na⁺ currents, T and L-type Ca²⁺ currents, as well as inward Na⁺-Ca²⁺ exchange current (regulated by intracellular Ca²⁺). Now Ju and Allen and colleagues have introduced another factor that is possibly involved in pacemaking: store-operated Ca²⁺ channels (SOCs).

SOCs are Ca²⁺ permeable channels; they are voltage-independent and, therefore, distinct from the voltage-dependent Ca²⁺ channels (Ca, channels). SOCs are activated by the emptying of intracellular Ca²⁺ stores, and the subsequent Ca²⁺ influx via the SOCs results in a refilling of the stores. SOCs are well known to be important Ca²⁺ influx pathways in nonexcitable cells, and there is accumulating evidence that they exist in excitable cells, including cardiac ventricular myocytes. Despite intense research, the nature of the Ca²⁺ sensor in the Ca²⁺ stores and the signal between the sensor and the SOCs is unknown. The identity of SOCs is still debated, but TRPCs are likely contenders. The TRP (transient receptor potential) channel was first identified in Drosophila, in which it is involved in phototransduction. There are seven TRPC family members (TRPC1–7) in mammals, and there is evidence (some of which is controversial and disputed) that 6 of the TRPC channels are SOCs (the exception is TRPC6).

Ju et al report evidence (from RT-PCR) of transcripts for 6 of the 7 TRPC channels (the exception is TRPC5) in the sinoatrial node. Using immunocytochemistry, they show evidence of some of the TRPC channels at the protein level in sinoatrial node cells: TRPC1, TRPC3, TRPC4, and TRPC6. In particular, Ju et al show evidence of TRPC3 and TRPC4 proteins in the sarcolemma of sinoatrial node cells. Most impressively, Ju et al show functional evidence of SOCCs in the sinoatrial node: they show that, after store (ie, SR) depletion by removal of extracellular Ca²⁺, the restoration of extracellular Ca²⁺ results in a seemingly massive rise in intracellular Ca²⁺. The rise is most likely the result of Ca²⁺ influx—it is greatly increased by blocking SR Ca²⁺ uptake by

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cyclopiazonic acid. Blocking L-type Ca\(^{2+}\) channels (by nifedipine) or the Na\(^{-}\)-Ca\(^{2+}\) exchanger (by KBR7943) has little or no effect on the Ca\(^{2+}\) influx signal, whereas it is greatly reduced by the SOCC blockers (admittedly, not specific), Gd\(^{3+}\) and SKF96365. Ju et al\(^{3}\) suggest that SOCCs, as well as being involved in Ca\(^{2+}\) handling in the sinoatrial node, may carry a significant inward current, because when they applied the SOCC blocker, SKF96365, pacemaking was significantly slowed. Furthermore, they suggest that there may be a complex interaction between SOCCs, the SR, and Na\(^{-}\)-Ca\(^{2+}\) exchange. For example, cyclopiazonic acid is expected to cause a decrease in the SR Ca\(^{2+}\) content and, therefore, a decrease in SR Ca\(^{2+}\) release and, therefore, a decrease in inward Na\(^{-}\)-Ca\(^{2+}\) exchange current. This is expected to slow pacemaking. However, the decrease in SR Ca\(^{2+}\) content is expected to increase inward SOCC current, and this will oppose any slowing of pacemaking as a result of the decrease in inward Na\(^{-}\)-Ca\(^{2+}\) exchange current.

It is possible that SOCCs are more important in the sinoatrial node than in the working myocardium—whereas Ju et al\(^{3}\) measured substantial SOCC-mediated Ca\(^{2+}\) influx in all sinoatrial node preparations, Nakayama et al\(^{13}\) only observed a “very subtle” SOCC-mediated Ca\(^{2+}\) influx (measured using a comparable protocol) in 25% of mouse, presumably ventricular, myocytes. If SOCCs are more important in the sinoatrial node, this would be a difference in Ca\(^{2+}\) handling between the sinoatrial node and the working myocardium. Such a difference would not be a surprise, because Ca\(^{2+}\) handling in the sinoatrial node and the working myocardium has been shown to be different in many other respects (Figure). As compared with working myocardial cells, cells from the center of the sinoatrial node:

1. are small and, therefore, their surface area:volume ratio is high—sarcolemmal fluxes of Ca\(^{2+}\) may, therefore, be more influential (Figure, A);
2. lack t tubules;
3. only have subsarcolemmal SR—for example, they lack the corbular SR characteristic of atrial cells (Figure, A);4. express the L-type Ca\(^{2+}\) channel isoform, Ca\(_{1.3}\), as well as or instead of Ca\(_{1.2}\);5. possibly have a lower expression of SERCA2a (SR Ca\(^{2+}\) pump), RYR2 (SR Ca\(^{2+}\) release channel), and NCX1 (Na\(^{+}\)-Ca\(^{2+}\) exchanger)\(^{14,15}\);6. express RYR3 as well as RYR2;7. possibly have a higher diastolic intracellular Ca\(^{2+}\) concentration and smaller intracellular Ca\(^{2+}\) transient\(^{16}\); and8. have a high intracellular cAMP concentration resulting in oscillatory Ca\(^{2+}\) release from the SR (to facilitate pacemaking).\(^{17}\)

In conclusion, Ju et al\(^{3}\) have introduced a new family of channels, the TRPCs, which may play a role in both Ca\(^{2+}\) handling and pacemaking in the sinoatrial node. Of course much remains to be done. Perhaps the most urgent task is to measure SOCC current and function in single sinoatrial node cells. So far, familial (ie, hereditary) sick sinus syndrome (sinoatrial node dysfunction) in patients has been linked to mutations in HCN4 and Na\(_{1.5}\).\(^{10}\) If SOCCs and other Ca\(^{2+}\) handling proteins are important in pacemaking, it is possible that these too will be linked to familial sick sinus syndrome.

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None.

**References**


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