Normal cardiac impulse initiation occurs in the sinus node, in which gradual depolarization during phase 4 of the transmembrane potential results in attainment of threshold and initiation of action potentials that propagate to the rest of the heart. A current referred to as $I_f$ initiates phase 4 depolarization. This current activates on hyperpolarization following termination of a preceding action potential. Although $I_f$ initiates phase 4 depolarization, it is not the only current contributing to this: inward currents carried by Ca also play a role as does the Na/Ca exchanger. Counteracting these depolarizing influences are hyperpolarizing, outward currents carried by K. It is generally accepted that any net increase in inward current or decrease in outward current will increase phase 4 depolarization and cardiac rate.

A key property of the pacemaker current is its modulation by autonomic influences. Catecholamines increase sinus rate by pathways initiated via their binding to beta-1 adrenergic receptors. This binding activates a G-protein coupled pathway in which adenyl cyclase metabolizes ATP to cyclic AMP and P. The cyclic AMP binds to specific sites near the carboxy terminus of the channel, resulting in increased channel activation and an increased pacemaker potential. The effect of catecholamines to activate the channel is counteracted by muscarinic agonists, such as acetylcholine. The pathway here, too, is mediated via a G protein, with the net result being a braking of catecholamine-induced actions to accelerate rate.

The property of the channel to be activated on hyperpolarization and to bind cyclic AMP has led to the nomenclature: hyperpolarization-activated, cyclic nucleotide-gated (or HCN) channel. There are four HCN channel isoforms; three, HCN1, HCN2 and HCN4 are in heart. HCN3 is in neural tissues. HCN4 and HCN1 contribute to impulse initiation in the sinus node. It has long been appreciated that in a variety of settings it might be desirable to either slow or speed heart rate. Major areas in which slowing of heart rate is often desirable include ischemic heart disease and a variety of post-surgical settings. A primary means for slowing rate has been beta-adrenergic blockade: yet this carries a potential for deleterious effects such as a loss of inotropy. For this reason, agents that act primarily on the HCN channel as a target to reduce $I_f$ and slow rate on that basis have been viewed as desirable. In contrast to many other pharmacological agents, ivabradine has high selectivity and specificity for its target, the HCN channel. Importantly, in blocking the HCN channels that carry $I_f$, ivabradine suppresses but does not stop the sinus node pacemaker’s rate of firing. This reflects the contribution of the other ion channels mentioned above to the pacemaker potential, and also provides an important safety factor for ivabradine. Ivabradine’s clinical success to date provides an example of how highly targeted therapy can result in a risk/benefit advantage over other effective therapies.

Another area of interest with regard to modulating $I_f$ is in settings in which one might want to increase heart rate. The classic example here is the bradycardias that accompany sinoatrial node dysfunction or high degree atrioventricular block. Whereas the standard therapy over the past 60 years has become electronic pacemakers, over the last 5-10 years interest in biological pacemaking as an adjunct or alternative has increased. Although a variety of approaches were tried initially, current attempts focus largely on the use of viral and/or stem cell-based gene and cell therapies to deliver $I_f$ current. The obstacles relating to the use of viral vectors or stem cells in humans constitute formidable challenges, yet preclinical research has proceeded briskly. This has demonstrated that the biological pacemaker is not only capable of providing baseline pacemaker function, but is autonomically responsive and can interact well with electronic pacemakers in a tandem mode of therapy.

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.
A Tale of Two Arrhythmias
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I will give a brief overview of the history of two arrhythmias in which the atrioventricular (AV) node is involved.

1. Atrioventricular reentrant tachycardia.

After describing circulating excitation in ring-like preparations of hearts of a variety of species, G.R. Mines (1) wrote in 1913: “I venture to suggest that a circulating excitation of this type may be responsible for some cases of paroxysmal tachycardia as observed clinically”. One year later, he repeated this suggestion after reading Stanley Kent’s description of a connection between the right atrium and the right ventricle (2). “Supposing that for some reason an impulse from the auricle reached the main A-V bundle but failed to reach this “right lateral” connection, it is possible that the ventricle would excite the ventricular end of this right lateral connection, not finding it refractory as it normally would at such a time. The wave spreading up to the auricle might be expected to circulate around the path indicated.” (3)

This was written 16 years before Wolff, Parkinson and White described the clinical syndrome that now bears their name (4), 18 years before Holzmann and Scherf (5) ascribed the abnormal ECG in these patients to pre-excitation of the ventricles via an accessory AV bundle, 19 years before Wolferth and Wood (6) published the first diagrams showing the pathway for orthodromic and antidromic reentry, and 53 years before the first studies quoted Mines.

The era of surgical ablation of the accessory pathway started in 1967, and was initially hampered by not realizing the correct anatomy of the accessory pathway, which was quite different from what Kent had described (2). In 1944 Öhnell showed that the accessory bundle did not penetrate the fibrous annulus, but coursed in the epicardial fat surrounding the coronary arteries. After Sealy and colleagues in 1976 developed a “fish hook” to scrape through the epicardial fat, surgical treatment became successful. It also paved the way for the hugely successful catheter ablation.

2. Atrioventricular nodal reentrant tachycardia.

Mines (1) also was the first to describe AV nodal reentry, which he called a reciprocating rhythm. He postulated that the different fibres in the AV node “are ordinarily in physiologic continuity, yet it is conceivable that exceptionally, as after too rapid stimulation, different parts of the bundle should lose their intimate connection… A slight difference in the rate of recovery of two divisions of the A-V connection might determine that an extrasystole of the ventricle, provoked by a stimulus applied to the ventricle shortly after activity of the A-V connection, should spread up to the auricle by that part of the A-V connection having the quicker recovery process and not by the other part. In such a case, when the auricle became excited by this impulse, the other portion of the A-V connection would be ready to take up transmission again back to the ventricle… the condition once established would tend to continue, unless upset by the inter-

polution of a premature systole’’ (1). It took more than half a century before upsetting AV nodal reentry by “premature systoles’ was accomplished in patients and in isolated rabbit heart preparations. Both papers did quote Mines.

Although all authors working on AV nodal reentry agree that that the lower level of the junction of antegrade and retrograde pathways is above the level of the His bundle, controversy has existed regarding the question whether or not the atrium forms part of the reentrant circuit. The fact that it is possible, both by surgery and catheter ablation, to abolish AV nodal reentry by destroying tissue far away from the compact AV node whilst preserving AV conduction seems clear evidence that the atrium must be involved. However, in the canine heart the reentrant circuit during atrial and ventricular echo beats is confined to to the compact node and regions immediately adjacent to it, and atrial tissue is not involved. To quote Zipes, who borrowed the words that Churchill used to characterize Russia: “The AV node is a riddle wrapped in a mystery inside an enigma”.


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