

**Noble D & Tsien R W.** The kinetics and rectifier properties of the slow potassium current in cardiac Purkinje fibres. *J. Physiology* 195:185-214, 1968.  
[University Laboratory of Physiology, University of Oxford, England]

The kinetics of a slow conductance mechanism activated in the pacemaker range of potentials in Purkinje fibres were determined with sufficient accuracy to reproduce the time course of variation during the pacemaker depolarization itself. The reversal potential of the net current change was shown to vary with external potassium in the way expected for a pure potassium current. [The  $SC/8$  indicates that this paper has been cited in over 380 publications.]

## The Cardiac "Pacemaker" Current

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The sequel to this paper is at least as important as its origins. Its origins lay in the search for experimental evidence for the theory that pacemaker rhythm in the heart is generated by decay of a potassium conductance. It was already known that slow channel gating occurs at very negative potentials within the pacemaker range, so the major question was whether the kinetics and other properties were quantitatively sufficient. We found that they are and that it was possible to use the experimental data to reconstruct the time course of gating during the pacemaker potential.

The reasons for the frequent citing of this paper are first that it seemed to provide the final quantitative proof of the potassium conductance decay model, and second that it was

the first to provide a complete kinetic analysis of the gating of a cardiac channel. Moreover, it led to the demonstration that transmitters like adrenaline could modulate electrical activity by shifting the voltage dependence of the gating.<sup>1</sup>

Despite the success in using the data in this way, there were important loose ends in the work. The first was that the current disappears in sodium-free solutions. The second was that the reversal potentials at various external potassium levels were all a few mV more negative than predicted. The loose ends have turned out to be of the utmost importance. The discrepancy between observed and predicted reversal potentials was confirmed by later work,<sup>2</sup> while this and the sodium dependence became the cornerstones from which D. DiFrancesco<sup>3</sup> showed that the channel is in fact a sodium-potassium channel activated by hyperpolarization. A full account of the fascinating way in which these apparently minor details became the central features of a new theory will be found in a recent review,<sup>4</sup> and it illustrates the importance of reporting the raw data and of noting discrepancies. However convincing one's interpretation may be, one can never know how important the discrepancies may become.

Although the Purkinje fibre pacemaker potential is now attributed to slow activation of sodium entry, the potassium decay model is still the preferred one for the natural cardiac pacemaker: the sinus node. In an immediate sequel to the cited paper, O. Hauswirth, D. Noble, and R.W. Tsien<sup>5</sup> demonstrated the essential features of this mechanism in an early experimental model: the depolarized Purkinje fibre. The fact that Purkinje fibres could show very different pacemaker activity over different voltage ranges, one of them closely resembling that of the sinoatrial node, was the first major clue that not all pacemaker mechanisms in the heart are similar. Since then, even more mechanisms have been discovered, the most important being the arrhythmogenic current first analysed by W.J. Lederer and Tsien.<sup>6</sup>

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2. Cohen I, Daut J & Noble D. The effects of potassium and temperature on the pacemaker current,  $i_{K1}$ , in Purkinje fibres. *J. Physiology* 260:55-74, 1976. (Cited 55 times.)
3. DiFrancesco D. A new interpretation of the pacemaker current  $i_{K1}$  in Purkinje fibres. *J. Physiology* 314:359-76, 1981. (Cited 165 times.)
4. Noble D. The surprising heart: a review of recent progress in cardiac electrophysiology. *J. Physiology* 353:1-50, 1984. (Cited 160 times.)
5. Hauswirth O, Noble D & Tsien R W. The mechanism of oscillatory activity at low membrane potentials in cardiac Purkinje fibres. *J. Physiology* 200:255-65, 1969. (Cited 120 times.)
6. Lederer W J & Tsien R W. Transient inward current underlying arrhythmogenic effects of cardioactive steroids in sheep cardiac Purkinje fibres. *J. Physiology* 263:73-100, 1976. (Cited 100 times.)

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