Sodium Channel Blockade
as an Antiarrhythmic Mechanism

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Despite the increasing use of implantable devices and ablative procedures, drugs remain the mainstay of therapy for cardiac arrhythmias. The local anesthetic-class drugs are the most widely prescribed antiarrhythmic agents. They exert their antiarrhythmic effect by blockade of the inward sodium current [1]. The adverse impact of drug treatment on survival of patients in Cardiac Arrhythmia Suppression Trial and in patients with atrial fibrillation have forced serious reconsideration of the indications for and selections of drugs [2, 3]. The trial results have also provided a strong impetus for the study of the basic mechanisms of action of these drugs. Such studies may relate basic mechanisms of action to proarrhythmic potential and ultimately lead to safer, more effective treatment. This paper reviews the normal function of the sodium channel, the mechanism(s) of its blockade by drugs and the implication of the blocking mechanisms to the clinical use of these drugs.

Cardiac Sodium Channel Function

The inward current carried by sodium ions sustains propagation in the atrium, His-Purkinje system and ventricle. The sodium ions that enter the cell during depolarization also contribute to excitation-contraction coupling. By competing with intracellular calcium for sites on the Na/Ca exchanger, sodium ions decrease calcium ion extrusion and enhance cardiac inotropy [4]. Conversely, agents that block the sodium channel are predicted to have a negative inotropic effect. The sodium channel is a member of the class of integral membrane proteins that permit the rapid and selective movements of ions across the cell membrane. Recent biophysical and molecular biological techniques have shed considerable light on the function of the sodium channel [5–7].

The classic studies of Hodgkin and Huxley in nerve axons provide the basis for the theoretical framework of sodium channel function [8]. They postulated three conductance states of the sodium channel: a closed conformation – the resting state – occupied at normal membrane potentials, an open conformation – the activated state – having high conductance to sodium ions and occupied during depolarization, and a non-conducting conformation – the inactivated state – occupied at depolarized potentials (summarized in Fig. 1). To account for the transient nature of the premeability change, Hodgkin and Huxley proposed that ion conduction by the sodium channel was controlled by independent activation (m) and inactivation (h) gates. In the resting state, the activation gate is closed and the inactivation gate is open. Membrane depolarization opens the activation gate and
with both gates open, sodium ions move into the cell down their electrochemical gradient. With maintained depolarization, the inactivation gate closes and terminates the inward sodium movement. To restore the sodium conduction ability, the membrane must be repolarized to the resting range of potential. The recording of small outward gating currents preceding the rising phase of the sodium current provided strong support for the Hodgkin-Huxley model [9].

Macroscopic and single channel current measurements introduced during the past decade have enabled direct examination of the Hodgkin-Huxley model of

Fig. 1. The Hodgkin-Huxley model of sodium-channel gating. Upper and middle panels, facsimiles of a step change in membrane potential, $V_m$, and the resulting current, $I_m$. Lower panel, Ion movement through the channel is controlled by activation ($m$) and inactivation ($h$) gates. In the resting state, the $m$ gate is closed and the $h$ gate is open. A step change in membrane potential moves the $m$ gate to the open position and with both gates open, sodium ions move into the cell generating an inward current. However, with maintained depolarization, the $h$ gate closes, terminating ion movement. Immediately following repolarization, $m$ and $h$ gates are closed. With time the channels return to their resting state (recover from inactivation) with the $m$ closed and $h$ gate open.

Fig. 2A–C. The kinetic properties of cardiac sodium channels. A The nomenclature used to describe single channel currents. Upper trace, voltage step from $-120$ to $-60$ mV; middle and lower traces, the current responses to the voltage step in successive trials. After a delay (asterisk) downward deflections represent the opening of single sodium channels. Lower trace, there are no openings and the response is termed a null. B, C shown current responses during depolarizing steps to $-60$ and $-40$ mV. Lowest trace, the current obtained by averaging the current during 200 steps. B, Channel openings occur after a long and variable delay. Some channel openings occur at a time when the average current is declining. C The latency is brief; the decline in the average current parallels channel closure. The vertical calibration is 2 pA for the upper five traces and 0.75 pA for the average current (trace 6). The horizontal calibration is 10 ms. Currents were filtered at 2.5 kHz and sampled at 20 kHz. The temperature was $22\, ^\circ\text{C}$