CHAPTER 2

Classification of Antiarrhythmic Actions

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A. Functions of Selective Ionic Currents

In cardiac cells there are four main sources of EMF, as noted in the preceding chapter, engendered by concentration differences across the cell membrane of Na, Ca, K and Cl ions, which would be in equilibrium at intracellular potentials of approximately +56, +120, −94 and −40 mV respectively. In order that current from these sources may be used for physiological functions, ion-selective pathways through the membrane can be opened and closed. The function of sodium current is to depolarize atrial and ventricular muscle cells and Purkinje cells, and of calcium current to depolarize nodal cells. Slow depolarization in the central SA node cells permits faster depolarization in the surrounding transitional cells, when they reach threshold, to overtake them and synchronize firing of the node as a whole, from which a ring of excitation spreading outwards in all directions. Slow depolarization of the AV node provides the delay of conduction required while blood is transferred from atrium to ventricle. Calcium current is also involved in excitation-contraction coupling, and can be increased by the opening of an additional set of pathways under the control of adrenergic stimulation. The main function of potassium current is repolarization, but the function of chloride current is uncertain. High Cl permeability in P cells (pale sinoatrial node (SAN) cells) may provide a sink for depolarizing neighbours in the pacemaking process. Chloride-bicarbonate exchange may be concerned in the control of intracellular pH (Vaughan-Jones 1979).

The existence of selective ion channels with different functions offers the possibility of pharmacological modulation, and groups of drugs have been developed capable of restricting with varying degrees of selectivity sodium, potassium and calcium currents in the heart. There is some evidence that restriction of chloride current may be involved in the action of the “specific bradycardic agents” (SBAs, Chap. 19), but this is unproven. Calcium channels dependent on adrenergic stimulation can be modulated by antisympathetic drugs.

During the past 15 years antiarrhythmic drugs have been presented at a frequency of one new compound every few months. Some were developed for quite different roles—mexiletine, for example, as an antiepileptic, melperone as a tranquillizer—and were later discovered to have antiarrhythmic properties in the heart. All of them, however, with a single exception, the SBAs, have been found to possess one or more of four actions upon which a classification
of antiarrhythmic actions was based originally in 1970, updated at intervals (VAUGHAN WILLIAMS 1970, 1980, 1981, 1984). Several of the drugs had more than one of the four actions, so that it deserves emphasis that the classification was not so much a categorization of drugs in relation to chemical structure or physical properties, but rather a description of four ways in which abnormal cardiac rhythms can be corrected or prevented. Drugs in the same class from the point of view of their antiarrhythmic action could appear very different in the total clinical environment, due to differences in kinetics of action, distribution, especially into the CNS, metabolism, and sideeffects unrelated to actions on the heart.

In experimental studies of antiarrhythmic actions two main strategies have been adopted. Abnormalities of cardiac rhythm can be induced in animals by a variety of procedures (aconitine, digitalis, barium, programmed stimulation, coronary ligation, etc.), and the effects of drugs investigated empirically. Unfortunately such procedures do not induce consistent results (Chap. 3) and, even if they did, doubt would still remain concerning the relevance of such artefacts to human cardiac arrhythmias. In this field the only important target is man. An alternative approach is to study the detailed electrophysiological and pharmacological actions of known antiarrhythmic agents in the hope of finding some common properties to which their efficacy could be attributed, and which might throw some light on the probable origin of the arrhythmias themselves.

**B. Class I Antiarrhythmic Action**

The first class of action was that exerted by quinidine and a number of other remedies (SZEKERES and VAUGHAN WILLIAMS 1962) which, at 10–100 times their antiarrhythmic concentrations, incidentally also behaved as local anaesthetics on nerves. These compounds, though differing in other respects, had in common the property of “interfering specifically with the process by which depolarizing charge is transferred across the membrane”, i.e. by fast inward sodium current. The effect was revealed as a depression of the maximum rate of depolarization (MRD), unless the interstimulus interval was so long that it permitted full recovery between beats (Chap. 1, Fig. 17). Sodium channels are rapidly inactivated after depolarization and remain in the inactivated state until repolarization proceeds to voltages more negative than about –55 mV. It was suggested that the (class I) drugs interfered with the process by which Na channels were “reactivated in response to repolarization” and that in consequence they “extended the effective refractory period to a point long after the time at which repolarization was already complete”. The concept that these drugs were combined with the sodium channels in their inactivated form (i.e. after depolarization) was supported by the very early finding that the compounds were more potent the shorter the diastolic interval, as already noted.

That this, historically the first, class of action was responsible for the antiarrhythmic effects was not universally accepted, and BIGGER and MANDEL (1970) concluded from their own work “the results caused us to reject the hy-