Current perspectives

Electropharmacological effects of antiarrhythmic drugs on atrial fibrillation termination. Part I: Molecular and ionic fundamentals of antiarrhythmic drug actions

Leonardo Calò, Luigi Sciarra*, Filippo Lamberti, Maria Luisa Loricchio, Antonio Castro, Leopoldo Bianconi, Claudio Pandozi, Fiorenzo Gaita**, Massimo Santini

*Department of Cardiac Diseases, San Filippo Neri Hospital, Rome, *Department of Cardiology, Conegliano Hospital, Conegliano (TV), **Department of Cardiology, Mauriziano Hospital, Turin, Italy*

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In the last few years many studies have been performed with the aim of gaining a better understanding of the pathophysiological nature of atrial fibrillation. These recent observations provide new insights into the initiation and perpetuation of atrial fibrillation, underlying the importance of the pulmonary veins as major sources of atrial triggers and introducing new concepts such as the atrial electrical remodeling and the spatial heterogeneity of the electrophysiological characteristics of this arrhythmia. The increasing knowledge about the cardiac ion channel structure and function and about the electrophysiological actions of the antiarrhythmic drugs may contribute to a better comprehension of the mechanisms of the pharmacological termination of the arrhythmia. In part I of the review we try to give a unified vision of the old models and new concepts about the molecular and ionic fundamentals of antiarrhythmic drug actions.

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Address:
Dr. Leonardo Calò
Via della Pedica, 348
00046 Grottaferrata (RM)
E-mail: leonardo.calo@tin.it

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice. The restoration and maintenance of sinus rhythm are the main objectives of therapy. Since the first observations of Lewis[1] with quinidine in 1922, antiarrhythmic drugs have been widely used to convert AF. Nevertheless, the arrhythmia still remains a challenge to pharmacological therapy. Experimental observations of the mechanisms of action of the antiarrhythmic drugs in AF are limited and several aspects of this important issue are still not completely clear. Recent improvements in molecular and genetic sciences have provided new insights into the structure and function of the cardiac ion channels. Together with a better knowledge of the electrophysiological mechanisms of AF, these insights may contribute to a better comprehension of the mechanisms of action of antiarrhythmic drugs in terminating AF.

Cardiac ion channels

The cardiac myocyte is electrically insulated from the surrounding milieu by the lipid bilayer of the sarcolemma. The ion channels are proteins spanning into the membrane with water-filled pores that allow the passage of ions along their concentration gradient. These proteins can change their three-dimensional conformation and thus control ion movement in response to the influence of the voltage changes (voltage-operated channels or gated channels), and to the action of neurotransmitters and other substances (receptor-operated channels). The protein channels are selective and favor the passage of one ion over another. The different permeability of anions and cations across the membrane, with the predominance of K^+ conductance in resting conditions, determines a prevalence of negative charges inside the myocyte and thus an internal negative resting of 80-90 mV. The gated channels change their conformation under the influence of the electric field and time, and, when open or closed, they

permit or prevent the passage of ions across the membrane. These changes of the conductance of selective ions determine the time-dependent action potential. The antiarrhythmic drugs can interact with the cardiac ion channels reducing the ionic conductance, with the Na^+, K^+, and Ca^{2+} channels as the principal targets. The dynamic interactions between such drugs and the ion channels are responsible for the main electrophysiological effects of the antiarrhythmic agents.

The sodium channel and sodium current. The Na^+ channels are responsible for the rapid upstroke of the cardiac action potential and for the fast transmission of excitation throughout the specialized conducting system as well as in the atrial and ventricular muscle fibers. Thereby, the role of Na^+ channels is fundamental in cardiac electrophysiology and in the genesis of arrhythmias as well as in antiarrhythmic pharmacology. The earliest observation of Na^+ channel activity dates back to 1952, when Hodgkin and Huxley[2] published a crucial work providing a rationale for the process of gating (opening and closing of the channel) and of ion permeation throughout the membrane. Later, Na^+ channels were the first voltage-gated ion channels to be cloned and sequenced[3], introducing the era of molecular manipulation and genetic techniques and of patch-clamp development[4]. The Na^+ channel structure[5,6] is quite complex and consists of various subunits. The principal one is the α-subunit, while the β-subunits are known to be important modulators of the Na^+ channel, but they seem to play a minor role in cardiac Na^+ channels. In figure 1 we illustrate the general concepts of the α-subunit structure[7-10]. The α-subunit of the Na^+ channel consists of four homologous domains (labeled I to IV). Each domain consists of six segments that cross the membrane (S1-S6), and is singularly very similar to a voltage-gated K^+ channel. The four domains are attached to one another thus forming a central pore. The critical role in determining the permeability or block of the pore is played by the residues between the fifth and sixth subunits of each domain. These residues describe a structure called "P-loop" because they turn back into the membrane lining the pore. The primary structure of the P-loops of each domain is unique. The P-loop asymmetries are responsible for the permeation characteristics of the channel. The selectivity for Na^+ in the Na^+ channel is particularly linked to the presence of a lysine in the filter region of domain III[7-9] and to domain IV in which mutations of various contiguous residues render the channel non-selective among different univalent cations[7]. It is still not completely clear how these residues can favor the specific permeation of Na^+ by a factor of at least 100:1 over other cations. Pairs of cysteine residues engineered into the P-loops of domains I and II can form internal disulfide bridges in a specific pattern which would have been unachievable unless the molecule was substantially mobile. Although the precise relationship between pore flexibility, permeation and selectivity is not completely understood, it is interesting to consider that cross-linking of an internal disulfide renders the molecule less Na^+ selective[10].

During the various phases of the action potential the Na^+ channel, responsible for the Na^+ current, cycles in three different states (gating process): a closed state, an activated state and an inactivated state. In figure 2 we schematically illustrate the Na^+ channel-gating process[11-25]. During phase 4 of the action potential (Fig. 3), at rest, the channels are closed. During phase 0 the Na^+

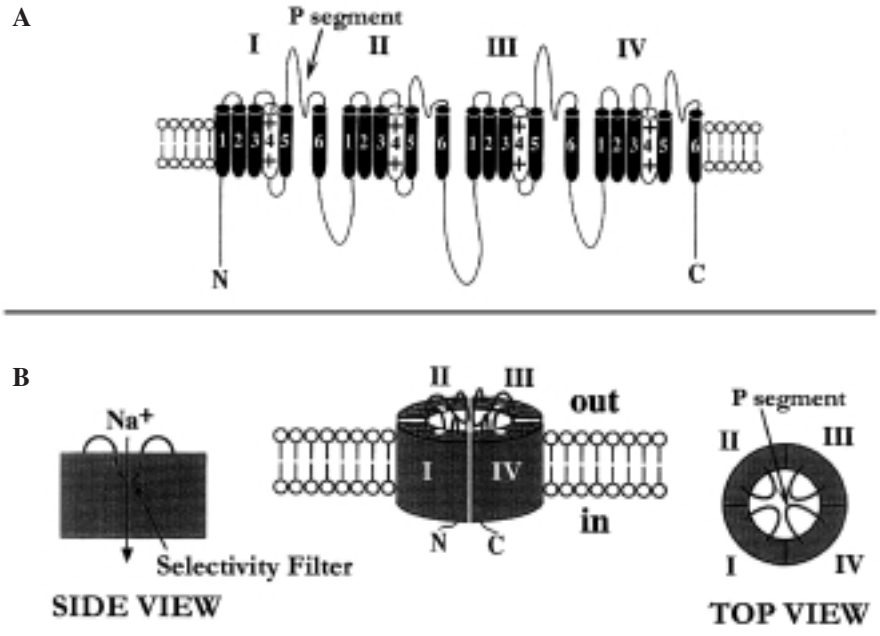

Figure 1. *Molecular structure of the α-subunit of the Na^+ channel.*

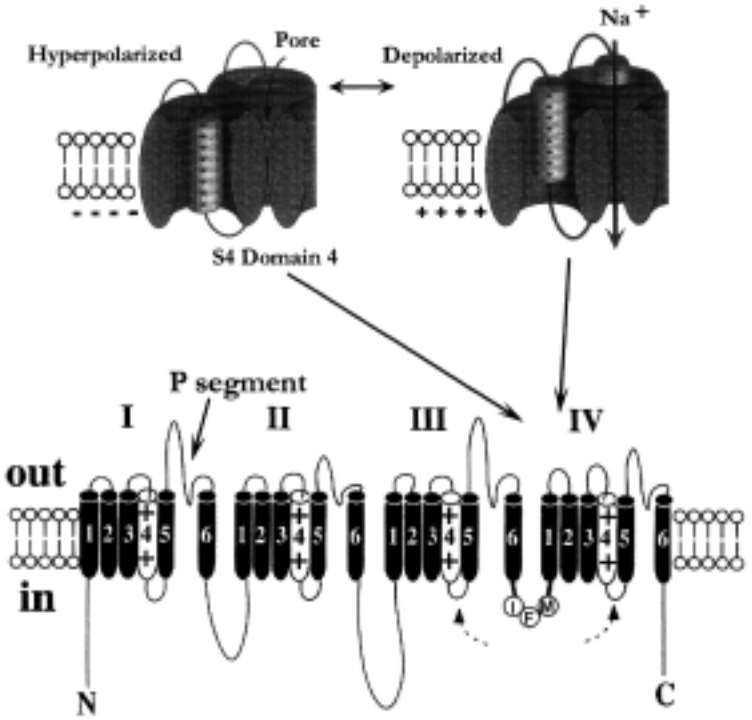

Figure 2. *Na^+ channel gating process. The four S4 segments are generally known to function as activation sensors. In the process of activation, charged residues of the S4 segment traverse the membrane through a narrow cuff formed by other regions of the channel[11-13]. The contributions of each S4 segment to activation are asymmetrical. Moreover, it has been observed that the activation and inactivation are coupled[14,15]. The time course of current decay reflects the voltage dependence of activation[16], although even microscopic inactivation varies in response to voltage[17,18]. While the S4 segments are considered to be the voltage sensors, mutational studies with local anesthetics[19-21], as well as the findings in K^+ channels, indicate that the S6 segments are likely to be the physical activation gate. It has been proposed that the receptor for local anesthetics is in the S6 segment of domain IV, and is responsible for a voltage-dependent block of the Na^+ channel[19]. The inactivation process, distinguishable in a fast and a slow inactivating process, is quite complex, even though knowledge in this field is on the increase. In particular, the fast inactivation process seems to be mediated by a cytoplasmic linker between domains III and IV (labeled IFM in the figure)[22-25].*

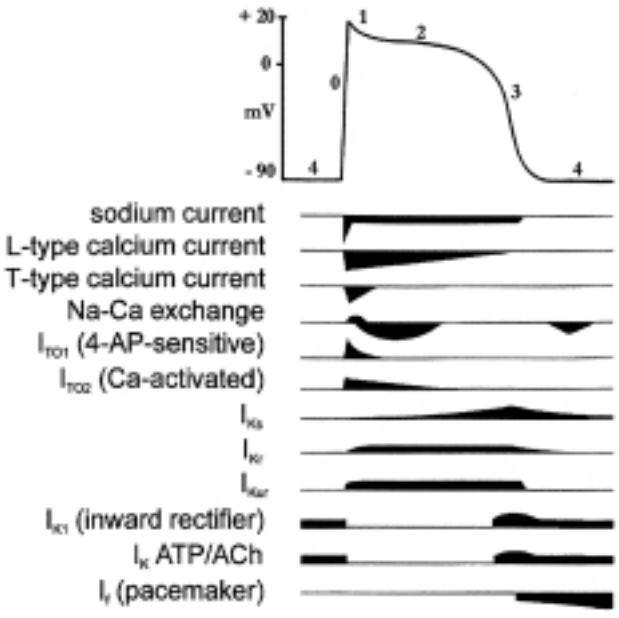

Figure 3. *Cardiac action potential in relation to the principal ionic currents. The action potential of the cardiac cell is determined by the voltage difference between the inside and outside of the cell as a function of time. The figure indicates the different phases of the action potential in correlation with the principal ionic currents that predominate during each phase. The currents under the lines are ionic inward currents; those over the lines are ionic outward currents.*

channels are in an open and conductive state. Shortly after the end of phase 0 the Na^+ channels return to an inactivated state that generally prevents them from reopening until the cell has repolarized to a potential of -60 mV. It has been proposed that the receptor for local anesthetics is localized in the S6 segment of domain IV, and is responsible for a voltage-dependent block of the Na^+ channel[19]. Blocking of the Na^+ currents is known to slow conduction throughout the ventricular and atrial myocardium and to reduce automaticity in specialized conducting tissue. It is interesting to observe that drugs blocking the Na^+ channel have a low affinity for the channel in the closed state, while the block is effective when the channels are opened or inactivated[26]. The kinetics of unblocking upon repolarization depends on the biophysical interaction between the drug and the channel, and is slow for class Ic antiarrhythmic drugs, intermediate for Ia, and fast for Ib. The Na^+ channel block is thereby influenced by the affinity of the drug for each channel state (open, inactivated or closed), by the heart rate (the block is greater at faster heart rates) and by the resting potential (a more depolarized state favoring the block). Ischemic tissue is known to have a higher affinity for the drugs, and both conduction slow-

ing and heterogeneous conduction have been linked to possible proarrhythmic effects in acute ischemia conditions[27-31].

The potassium channels and potassium currents. K^+ currents are carried by the most diverse family of cardiac ion channels and have a central role in cardiac electrophysiology. K^+ currents carry outward currents in the physiological range of potentials. They control the resting potential influencing the pacemaker function, and govern the action potential duration (APD). The inward Na^+ current causing the rapid upstroke of the action potential (phase 0) is followed by an early repolarization (Fig. 3) due to the outward K^+ flux through rapidly activating and inactivating K^+ channels. The plateau phase of the action potential (phase 2) depends on a fine balance between inward and outward currents. The inward currents are mainly due to a Ca^{2+} influx with a slow decline depending on L-type Ca^{2+} channel inactivation. The outward and hence repolarizing force is caused by the activation of multiple voltage-gated K^+ channels; the sequential activation of different K^+ channels over distinct time frames constitutes a complex system that ensures and controls the repolarization process. Table I shows the principal K^+ currents. Two types of voltage-gated channels play a major role in repolarization: transient outward (I_{TO}), and delayed rectifier currents (I_K). The I_K family includes several different components such as the ultra rapidly activating K^+ current (I_{Kur}), the rapidly activating current (I_{Kr}), and the slowly activating component (I_{Ks}). Other currents, such as the voltage-independent inwardly rectifying K^+ current, maintain or modulate the resting potential by governing the resting K^+ conductance; cardiac myocytes have several types of inward rectifier K^+ currents such as the quasi-instantaneous rectifier I_{K1}, the adenosine triphosphate (ATP)-inhibited I_{KATP} and the muscarinic receptor stimulated I_{KACh}. The principal K^+ currents, their role in the cardiac action potential and the genes that encode for the subunits of the channel are summarized in table I.

The successful cloning of the different subunits of the K^+ channels, as well as a better definition of the molecular structure and function of such channels, led to important progress in cardiac electrophysiology with remarkable implications even in clinical antiarrhythmic pharmacology. The voltage-gated K^+ channel was cloned for the first time from the Drosophila Shaker mutant[32]. Four main Drosophila subfamilies were described (Shaker, Shab, Shal, Shaw) and the first cloned mammalian K^+ channels were related to these subfamilies[33,34]. Other K^+ channels have been cloned in part on the basis of their involvement in congenital arrhythmias: Kv LQT1 and HERG. From these early and relatively recent observations, subsequent molecular studies about the K^+ channel structure and function had a tremendous development providing new complex and fundamental electrophysiological information[35-65]. The identification of multiple K^+ channels and the better comprehension of the physiologic role of the various K^+ currents in the heart provided evidence for the potential different electrophysiological effects of antiarrhythmic drugs more specific over one current than over another. Figure 4 is a schematic representation of the molecular structure of K^+ channel subunits.

The I_{TO} is activated by depolarization in the plateau range of the membrane potential and is involved in the early repolarization and notch of the action potential. Thereby, the I_{TO} influences the outward and inward ion flux during the plateau phase and modulates the APD[35].

The I_{Kur} describes the nearly instantaneous, depolarization-activated component of I_K[41] and is active in the plateau phase of the action potential. This current seems to play an important role in human atrial repolarization[41].

The I_{Kr} was initially defined as its sensitivity to block by the methanesulfonanilide class III antiarrhythmic agents such as E-4031 and dofetilide, and by d-sotalol[43-45]. The I_{Kr} is a small outward current during the initial plateau phase of the atrial and ventricular action potentials with a progressive increase in amplitude during terminal repolarization (Fig. 3). Moreover, the I_{Kr} is known to play an important role in pacemaker cells (E-4031 attenuates the maximum diastolic potential), to reduce the action potential amplitude, and to slow the rate of repolarization in rabbit sinoatrial nodal cells[46]. The chromosome 7-linked long QT syndrome LQTS2 has been related to mutations in HERG[53], a cloned gene[47] that encodes subunits of the human I_{Kr} channel. Extracellular K^+ modulates the block of the

Table I. Principal potassium currents.

Current name	Type of current	Related gene	Phase of action potential
I_{TO}	Transient outward	Kv4.2/4.3	Early repolarization and notch
I_{Kur}	Ultra-rapid delayed rectifier	Kv1.5	Plateau
I_{Kr}	Rapid delayed rectifier	HERG	Plateau; phase 2 and phase 3
I_{Ks}	Slowly activating delayed rectifier	KVLQT1+minK	Increase in plateau with slow deactivation
I_{K1}	Quasi-instantaneous inward rectifier	Kir2 family	Resting potential
I_{KATP}	Inward rectifier inhibited by ATP	Kir3.1+Kir3.4	Resting potential
I_{KACh}	Inward rectifier coupled to a G protein	Kir6.2+SUR1	Resting potential

ATP = adenosine triphosphate.

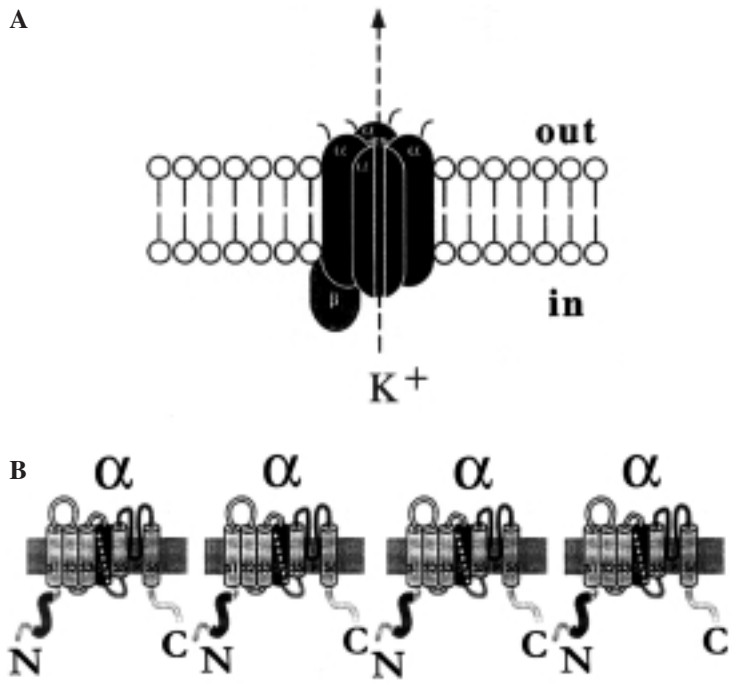

Figure 4. *Structure of voltage-gated K+ channel subunits.* Panel A: *three-dimensional reconstruction of a voltage-gated K+ channel. The coassembly of four α-subunits encodes the voltage-gated K+ channels. The β-subunit is a cytoplasmic protein that is supposed to influence the channel function.* Panel B: *schematic representation of the structure of the four α-subunits. Each subunit consists of six transmembrane segments (S1-S6). The voltage sensor of the channel is believed to be linked to the S4 segment. This segment can move in response to changes in the transmembrane voltage, causing conformational changes that open the channel. The P-loop is a sequence of amino acids between the fifth and the sixth segment. This structure functions as the ion conduction pathway of the channel.*

I_{Kr}. It has been observed that the action of block of drugs on the I_{Kr} is increased by low concentrations of extracellular K^+, whereas the elevation of the K^+ concentration, that occurs in myocardial ischemia or at rapid pacing rates, determines a low efficacy of drug block on the I_{Kr}[66]. This finding could explain the reverse use-dependent action of drugs that block the I_{Kr}, with a lower effect of block at rapid rates.

The I_{Ks} is characterized by a delayed and very slow activation[67]. The I_{Ks} gradually increases in amplitude during the plateau phase of the cardiac action potential (Fig. 3), with a slow deactivation that may have an important role in the rate-dependent shortening of the atrial and ventricular action potentials[67]. As the heart rate increases and the diastolic interval shortens, the I_{Ks} channels have less time to complete the deactivation process; thus, at faster rates the channels accumulate in an open state contributing to the shortening of repolarization. Mutations of the genes encoding for the I_{Ks} channel subunits are related to the long QT syndrome LQTS1[68].

The I_{K1} is an inward rectifier K^+ current that provides a very marked inward rectification. The I_{K1} carries a substantial current at negative potentials and hence sets a stable resting potential. During repolarization, this conductance is virtually shut down and other K^+ currents govern the repolarization process[35].

The *ATP sensitive K+ channel* (K_{ATP}) couples the membrane potential to the metabolic status. In fact, K_{ATP} channels are open when the ATP levels fall, and are inhibited by intracellular ATP. These channels play an important role in myocardial ischemia and other important non-cardiac physiologic functions such as insulin secretion[35].

The *muscarinic K+ channels* (K_{ACh}) mediate the slowing effect of the heart rate induced by parasympathetic activation. In sinoatrial and atrial cells, they open in response to parasympathetic stimulation. The K_{ACh} is an inwardly rectifying K^+ channel coupled directly to a G protein[35].

The calcium channels and calcium currents. Ca^{2+} channels are a complex family of proteins. Four types of Ca^{2+} channels are known to be present in the heart cells. Two of these, the L-type and T-type, are expressed on the surface membrane, and two (the sarcoplasmic reticulum Ca^{2+} release channel and the IP_3 receptor) are present on the internal membranes. The L-type Ca^{2+} channel protein constitutes the receptor for several drugs such as verapamil, diltiazem and nifedipine. For this reason when we generally speak of the Ca^{2+} channel in the heart, we consider only the L-type. We will focus our attention on the L-type and T-type Ca^{2+} channels because of their prominent role in the arrhythmogenesis.

The L-type Ca^{2+} channels are important both in normal and abnormal excitation. They are involved in the process of excitation both in the sinoatrial ad atrioventricular nodes. It is interesting to underline that in the

atrioventricular node the L-type Ca^{2+} channel exerts an excitatory effect on conduction; this provides evidence for the inhibitory effect of Ca^{2+} antagonists on atrioventricular conduction. Both in the working heart myocytes and in specialized conduction tissue this channel is responsible for the plateau current of the action potential. Thus, blockade of the L-type Ca^{2+} channel leads to a shortening of the action potential in such tissues. L-type Ca^{2+} channels also play important roles in arrhythmogenesis. They may mediate some inward currents that are known to favor early afterdepolarization, an arrhythmogenic mechanism responsible for some triggered arrhythmias[69,70]. Moreover, the slow conduction in reentrant circuits may be supported by L-type Ca^{2+} channels.

The voltage-gated L-type Ca^{2+} channel consists of various subunits: α_1, α_2, β, γ e δ (Fig. 5)[71]. The α_1 (165 kD), α_2 (130 kD), δ (28 kD), β (55 kD) and γ (32 kD) subunits are co-assembled together in a single voltage-gated L-type Ca^{2+} channel[72,73]. The α_1 subunit lines the central pore of the channel. The other subunits have a regulatory function, even though their precise role still has to be clarified. For our goals the most important subunit is α_1 (Fig. 5). In fact, it constitutes the central pore of the channel, contains the sequence believed to be fundamental to the voltage-dependent activation and it contains the receptor for the phenylalkylamines, the benzodiazepines and many dihydropyridine compounds. The whole subunity functions as an L-channel even though in an unregulated manner[74]. The α_1 subunit consists of the repetition of four domains that cross the membrane (I-IV). This structure is very similar to that of the Na^+ channel. Moreover, each domain consists of six different transmembrane segments. Segments 2-3 and 4-5 of each domain and segments 6-1 of domains I and II, II and III and III and IV are linked by other segments termed intracellular loops. On the other hand, segments 1-2, 3-4 and 5-6 of each domain are linked by extracellular loops. The segment 4 of each domain includes some residues with a positive charge; thus is believed to be responsible for the sensibility to the voltage. The loop sequence between segments 5 and 6 of each domain is called the "P-loop" (P from pore or permeation). The four P-loops of the respective domains are assembled together in the central structure of the channel and line the pore.

There is a high density of T-type Ca^{2+} channels in the sinoatrial and atrioventricular nodes[75]. This particular localization is consistent with the role of this channel in pacemaker cell function. Moreover, T-type Ca^{2+} channels have been implicated in cell growth, and they are present in high concentrations in the fetal heart[76] and in the early postnatal period[77]. Furthermore, experimental models of cardiac hypertrophy were associated

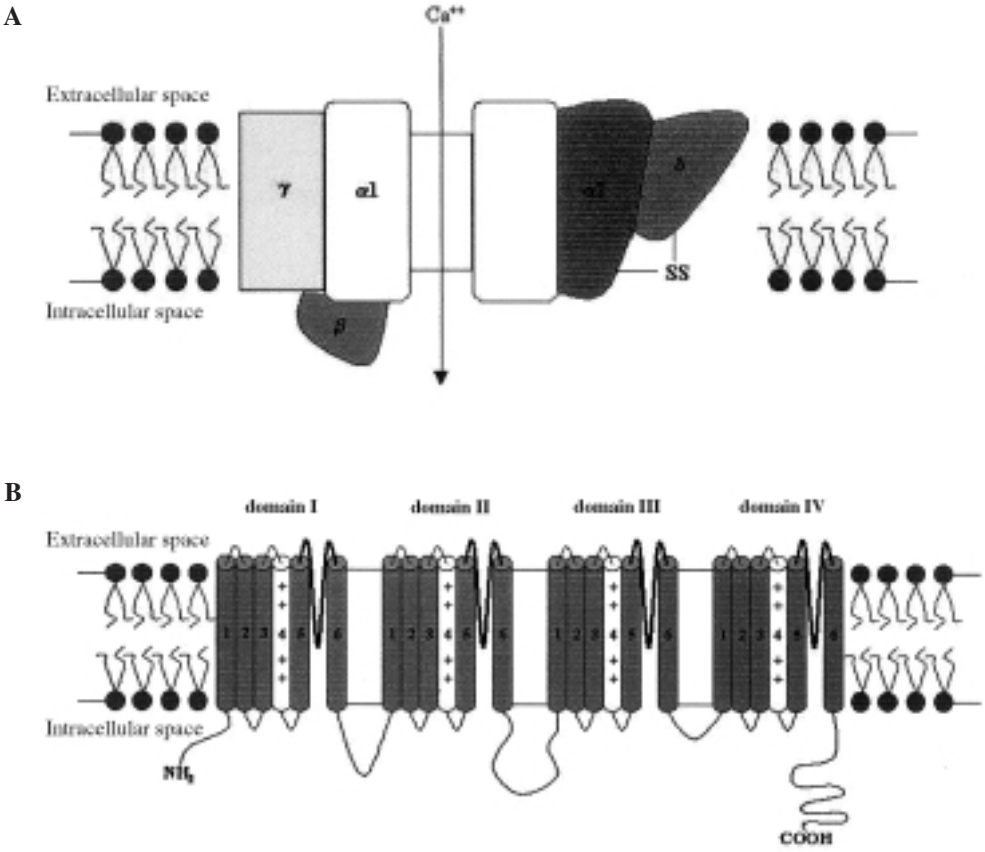

Figure 5. Panel A: *coassembled subunits of the voltage-gated L-type Ca^{2+} channel. From Catterall et al.[71], modified.* Panel B: *molecular structure of the α_1-subunit of the L-type Ca^{2+} channel.*

with a new expression of T-type Ca^{2+} channels in ventricular cells that usually do not show T-type currents[78]. Interestingly, treatment with mibefradil in a model of chronic heart failure in rats was associated with a longer survival[79]. The pharmacology of the T-channel has not yet been well defined. Several agents, including verapamil and diltiazem[80], affect the channel. The most selective agent on the T-type channel is mibefradil, even though its potential clinical utility has been compromised by serious drug interactions[81]. Despite the great efforts of research, the molecular structure of the T-type Ca^{2+} channel still has to be completely clarified, although cloning studies yielded important information even in this field.

The ionic specificity of antiarrhythmic drugs: relationships with their actions

The antiarrhythmic drugs vary consistently in their molecular and ionic specificity. Some agents, such as the I_{Kr} blockers dofetilide, E-4031, sematilide, almokalant, and d-sotalol are considered as being highly selective[82]; on the other hand drugs such as amiodarone seem to block a wide range of Na^+, Ca^{2+}, and K^+ channels[83]. We will consider only class Ia, Ic and class III agents (Table II), which are of particular interest owing to the mechanisms by means of which they terminate AF.

The principal electrophysiological effects of *quinidine*, as a class Ia antiarrhythmic drug in the modified Singh-Vaughan Williams classification, are the delay of conduction and the prolongation of repolarization. Quinidine exerts a use-dependent block of the fast Na^+ current I_{Na}, with a greater depression of the rapid upstroke of the action potential at faster rates[84]. The binding affinity of the drug, in fact, is higher for the activated state of the channel. Quinidine also blocks the I_K, the inward rectifier I_{K1}, the slowly inactivating tetrodoxin-sensitive Na^+ current (steady-state window current), the slow inward Ca^+ current I_{Ca}, the ATP-sensitive K^+ channel I_{KATP} and the I_{TO}[85]. The effects of the block of such K^+ currents explain the prolongation of the action potential. In atrial cells, quinidine blocks the acetylcholine-induced potassium current I_{KACh}[85]. Quinidine also blocks α_1 and α_2-adrenergic receptors[86,87]. The vagolytic effect is due to the muscarinic receptor block[85].

The electrophysiological properties of *disopyramide*, a class Ia antiarrhythmic drug, are very similar to those of quinidine. Disopyramide also exerts a use-dependent block on the I_{Na}. The recovery kinetics of the I_{Na} block are much longer than for the other class Ia agents[85]. Similarly to quinidine, disopyramide blocks the I_K, I_{K1}, I_{Ca}, and I_{TO} currents, and depresses the I_{KACh} in atrial cells[85]. The anticholinergic effect is due to the block of the muscarinic receptor.

Procainamide shares the use-dependent I_{Na} blocking effect with the other class Ia agents. In contrast to quinidine and disopyramide, procainamide only exerts a mild anticholinergic effect[85].

The class Ic antiarrhythmic drugs, such as *propafenone* and *flecainide*, markedly depress phase 0 of the action potential, have a considerable effect in slowing conduction and have only a slight effect on repolarization. The effect on the action potential prolongation of class Ic drugs is considerably lower than that of the class Ia agents. Flecainide and propafenone are potent use-dependent Na^+ channel blockers. Nevertheless,

Table II. Principal electrophysiological effects of classes Ia, Ic and III antiarrhythmic drugs.

Drug	Na^+ channel block	I_{Kr}	Other K^+ channel	Ca^{2+} channel block	β-blockade	Other actions
Quinidine	++	++	+	+		I_{KATP}, I_{KACh} and I_{K1} blockade I_{TO} blockade Muscarinic receptor blockade α-blockade
Disopyramide	++	+	+	+		I_{TO} blockade I_{KACh} blockade Muscarinic receptor blockade
Procainamide	++	+	+			Postganglionic sympathetic inhibition
Propafenone	++	+	+	+	+	I_{K1} and I_{TO} blockade at supratherapeutic levels
Flecainide	++	+	+	+		
Amiodarone	++	+	+	++		Non competitive β-blockade I_{K1} and I_{Ks} blockade
Sotalol		++			++	I_{K1} and I_{Na} blockade at supratherapeutic levels
Ibutilide		++				Slow plateau Na^+ current activation
Dofetilide		++				
Azimilide	+	+	++	+		I_{Ks} blockade

+ reported drug action that may contribute to clinical effects; ++ clinically important drug action.

their blocking effect also seems to be effective on K^+ currents such as the I_{Kr}, I_{K1}, I_{TO}[38,88] and also on the inward calcium currents[85].

The typical effect of a class III antiarrhythmic drug is the prolongation of the APD. With the only possible exception of ibutilide (see later), these agents prolong the APD by inhibiting the K^+ currents. Class III agents vary consistently in their selectivity for K^+ channel block, and some drugs, such as amiodarone, actually included in class III, are known to also block other ionic channels.

Amiodarone may be considered as an example of a non-specific antiarrhythmic drug. Initially it has been described as a relatively pure APD prolonging agent[89], and hence has been proposed as a class III antiarrhythmic drug. Nevertheless, subsequent studies demonstrated that amiodarone exerts effects pertaining to all four antiarrhythmic classes[83]. Amiodarone reduces the Vmax of the action potential[90,91] and the I_{Na}[92], suggesting a class Ib-like effect on an inactivated state of the Na^+ channel with rapid unbinding during diastolic potentials. It is also known that amiodarone, similarly to class II agents, produces non-competitive antagonism of the adrenergic effects on the heart[93,94]. The acute administration of amiodarone reduces the APD, whereas chronic administration prolongs it[90]. This effect, as well as the similarity between the effects of amiodarone and thyroidectomy[89], have led to the concept that the class III properties of the drug are linked to its antagonism of the thyroid effects on the heart myocytes. However, it has been recently clarified that the chronic use of amiodarone in guinea pig ventricular myocytes prolongs the APD by inhibiting the I_{Kr}, I_{Ks}, and I_{K1}, while hypothyroidism affects only the I_{Ks}[95]. This observation provides evidence for a direct class III effect of the drug on cardiac muscle. Finally, amiodarone is known to block the I_{Ca} in a time and frequency-dependent manner, similarly to the class IV antiarrhythmic agents[96,97].

The l-isomer of *sotalol* is over 50 times more potent as a β-blocker agent than the d-isomer[98]. Both isomers have class III activity consisting in the prolongation of the APD due to the block of the I_{Kr}[43,98,99]. The racemic sotalol displays β-blocking properties at lower concentrations than the class III effects[100,101]. Thus, in clinical use low-dose sotalol principally exerts β-blocking effects, while the class III effects are prominent at higher doses. The effects of sotalol on the prolongation of repolarization are reverse use-dependent in both atrial[102] and ventricular myocytes[103-105]. At higher concentrations, not of clinical relevance, sotalol can inhibit other currents such as the I_{K1} and I_{Na}[99].

Ibutilide is a class III antiarrhythmic agent available only for intravenous administration. The drug is a potent I_{Kr} inhibitor[106]. Moreover, ibutilide is also known to potentiate a slow plateau Na^+ current[107,108], an unusual mechanism of ionic action. Ibutilide as a class III agent, prolongs the APD and increases the atrial effective refractory periods. Even though reverse use-dependence is a common electrophysiological property of class III antiarrhythmic drugs that block the I_{Kr}, such as sotalol and dofetilide, the effect of ibutilide on the APD and effective refractory period did not seem to be related to the cycle length[109]. On the basis of this finding it was hoped that ibutilide would not have the significant proarrhythmic effects exerted by other class III agents at slow rates. Unfortunately, this hope was not confirmed by subsequent studies[110,111]. Furthermore, experimental studies showed that the effect of ibutilide in prolonging the QT interval and ventricular monophasic action potential is greater at longer than at shorter cycle lengths[112,113]. The rate dependence of the effects of ibutilide on the refractoriness of the atrial myocardium still remains to be completely elucidated, even though it has been observed that the drug can prolong the atrial effective refractory period at shorter cycles when compared to sotalol[114].

Dofetilide is a pure class III antiarrhythmic agent that selectively inhibits the I_{Kr}. The drug prolongs the effective refractory period and APD in both atria and ventricles without effects on conduction[115,116]. The drug's kinetics is characterized by a rapid onset and slow offset, and the reverse use-dependent effects on refractoriness have been observed mainly at high plasma concentrations[117].

Azimilide is a relatively new class III antiarrhythmic drug that was initially believed to be a selective blocker of the I_{Ks}[118]; further observations indicated that the drug also blocks other currents including the I_{Kr}, I_{Ca} and I_{Na}[119]. The drug is currently under review for approval for the control of AF. Azimilide is known to increase the atrial refractory period in a frequency-independent manner without significant effects on the conduction velocity[120].

The electrophysiological effects of class Ia, Ic and III drugs are summarized in table II.

Rate dependence of antiarrhythmic drug actions

The interaction between the drug and cardiac ion channel mainly depends on the concept that during the time course of the action potential the access to the receptor sites is intermittent. During the different physiologic phases of the channels, the antiarrhythmic drugs have different affinities for the receptor sites. Some drugs, such as the Na^+ channel blockers, exert a block that increases in amplitude with the repeated use or activation of the channel[121-123]. This effect is called use-dependent block and is characterized by an increased effect at faster rates.

Other antiarrhythmic drugs, such as many class III antiarrhythmic K^+ channel blockers, produce less block of the K^+ channels with an increased frequency of channel activation. Consequently, these agents are believed to be much more effective at blocking the K^+ channels

at slower rates. This effect is called reverse use-dependent block[82,124-126].

On the other hand, when the effect of block of an antiarrhythmic drug is not affected by the frequency, the term rate-independent block may be used.

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