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ADVANCES IN CARDIAC CELLULAR ELECTROPHYSIOLOGY: IMPLICATIONS FOR AUTOMATICITY AND THERAPEUTICS

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INTRODUCTION

The purpose of this review is to present a selected number of recent and interesting findings in the field of cellular cardiac electrophysiology. We focus on the cellular level, discuss membrane currents, and relate these currents to the genesis of arrhythmias and the actions of antiarrhythmic drugs. More specifically we consider TTX-sensitive plateau currents, the delayed rectifier current i_K, the background K current i_{K1}, as well as the pacemaker current i_f. We examine their contributions to normal automaticity in the ventricle and two types of triggered automaticity, the early afterdepolarization and the delayed afterdepolarization. We limit our discussions primarily to studies of "normal" as compared to "diseased" tissues, since the latter have been less well characterized.

TTX-Sensitive Plateau Currents

At least two TTX-sensitive sodium currents contribute to the action potential plateau in Purkinje fibers. The first of these currents, a time-independent

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sodium "window" current, is postulated to arise from the overlap of the activation and inactivation gating mechanisms of the sodium channel (1–4). The second of these currents, a time-dependent TTX-sensitive current, has been attributed to a slowly inactivating sodium current (5–7). It has been postulated that action potential shortening by some local anesthetic-type antiarrhythmic agents is due to blockade of these currents (3, 4, 6, 8). The window current may also contribute to the pacemaker potential (see below).

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The Delayed Rectifier i_K

From the initial studies of Hodgkin & Huxley (9) it was apparent that termination of the action potential was caused by activation of a delayed rectifier that was K^+ selective and provided the outward current necessary to repolarize the membrane. The first detailed study of the delayed rectifier in cardiac muscle was performed by Noble & Tsien (10). They suggested that two delayed rectifiers lie in parallel in the Purkinje fiber membrane; their corresponding currents were termed i_{x1} and i_{x2}. Both of these putative channels passed K^+ but were not very selective for K^+ over Na^+, and one did not possess instantaneous rectifier properties (i_{x2}).

Subsequent investigations have found a delayed rectifier in nodal, atrial, and ventricular tissue. By studying this current in isolated cells, the problems of K^+ fluctuations in narrow extracellular spaces have been eliminated (11, 12). Although the kinetic characteristics vary with cardiac location, it is now clear that the delayed rectifier is K^+ specific in all regions of heart. Consequently, we shall refer to the current through the delayed rectifier as i_K.

The delayed rectifier has been studied in rabbit nodal tissue where there appear to be two conductances (13) and in bullfrog sinus venosus where a single K^+-dependent conductance is present (14). The latter study suggested that the delayed rectifier was an important contributor to pacing as well as controlling the action potential duration.

Two recent independent studies of frog atrial cells have shown remarkable agreement in describing the properties of the delayed rectifier in this amphibian preparation (15, 16). The delayed rectifier is largely K^+ specific, composed of a single Hodgkin-Huxley conductance best described by a gating variable raised to the power 2 (also true for i_K of sinus venosus) and is half activated at -15 mV. The current-voltage relation for the open channel is linear, implying that the channel conductance is not voltage dependent. Initial voltage clamp studies from guinea pig ventricular myocytes suggest a delayed rectifier similar to that in atrium (17), although a detailed kinetic analysis was not reported.

The delayed rectifier in isolated Purkinje myocytes activates and decays as the sum of two exponentials (18). These kinetics are consistent with a single membrane channel with one open state and at least two closed states (18, 19).

The delayed rectifier is the major outward current activated during the action potential plateau in cardiac Purkinje fibers.

A question raised by previous investigations on multicellular preparations is whether the delayed rectifier is activated by intracellular [Ca^{2+}] (20). However, more recently, Ca^{2+} channel blockers nisoldipine (21) and $LaCl_3$ (16) have been shown to have very little effect, which suggests that Ca^{2+} influx is not essential to activate the delayed rectifier.

Ba^{2+} blocks i_K (19) but at much higher concentrations than necessary to block the time-independent inward rectifier i_{K1} (22). In Purkinje myocytes 1 mM Ba^{2+} results in only partial blockade of i_K. In guinea pig ventricular myocytes the quaternary ammonium derivative clofilium blocks i_K from the outside but has little effect on i_{K1} (33). Quinidine, but not lidocaine, dramatically reduces the magnitude of the delayed rectifier in rabbit Purkinje strands (8).

The differences in the reported properties of the delayed rectifiers in the different regions of heart suggest that differential action by pharmacologic agents on i_K may be possible. It will first be necessary to demonstrate that the observed differences are not entirely species dependent. A more detailed review of the cardiac delayed rectifier may be found elsewhere (24).

NORMAL AUTOMATICITY: THE PACEMAKER POTENTIAL

Following an action potential, there is a slow spontaneous depolarization in Purkinje fibers that is termed the pacemaker potential (also known as phase 4 depolarization or diastolic depolarization). This depolarization occurs as a result of a net inward current. We consider three of the currents involved in generating the pacemaker potential, namely (*a*) the inward current activated upon hyperpolarization, i_f, (*b*) the background K current i_{K1}, and (*c*) the steady state sodium "window" current.

I_f, The Inward "Pacemaker" Current Activated Upon Hyperpolarization

The i_f current (*a*) is activated by hyperpolarization, (*b*) is largely deactivated at −60 mV and largely activated at −90 mV, and (*c*) is selective to Na^+ and K^+ with a reversal potential between −20 and −50 mV in physiologic Tyrode's solution (25, 26). Diastolic depolarization in normal Purkinje fibers occurs between −90 and −60 mV. Since this voltage range is identical with that for activation of i_f, and since the kinetics of i_f are on the same time scale as the diastolic depolarization, i_f has been called the pacemaker current. The primary pacemaker in the sinus node is not thought to have a maximum diastolic more negative than −70 mV. Thus, although i_f contributes to pacing in this region, the dominance of its role is still being debated (27, 28).

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It appears that the i_f channel is of extremely small size, with a conductance of 1 picosiemens [70 mM K_o^+, 70 mM Na_o^+, (29)]. Raising $[K^+]_o$ increases the magnitude of the i_f conductance, while lowering $[Na^+]_o$ affects the ionic driving force but not its conductance. The fully activated i_f current appears linear at most external K^+'s with slight outward rectification at $[K^+]_o$'s ≤ 3 mM (25, 26).

The kinetics of i_f are complex. Following a step change in voltage, there appears to be an initial delay in activation, followed by a largely exponential activation at many potentials (30). At more negative potentials, a much slower component of activation is also observed (31). The more rapid component of activation has time constants ranging from hundreds of milliseconds to a couple of seconds, while the slow component is one to two orders of magnitude slower. Further in the middle of the activation range (-70 to -80 mV), activation and deactivation proceed with different time courses (32).

During the first few milliseconds of an action potential, i_f is rapidly deactivated by the upstroke and thus does not contribute to the balance of membrane currents during the action potential plateau. I_f begins to activate as repolarization proceeds more negative than -50 mV. However, because i_f activation kinetics are slow, i_f continues to activate throughout most of the diastolic depolarization. Thus i_f is a major contributor in the Purkinje strand to the inward current driving the membrane towards threshold.

Cs^+ blocks i_f current in a voltage-dependent manner, and is far more effective at hyperpolarized potentials (33). Ba^{2+} also blocks i_f but to a lesser degree (31). Lidocaine and quinidine also block i_f (6).

I_f is modulated by beta-agonists and acetylcholine, but apparently not by alpha-agonists (34–36). Beta-agonists shift the activation curve to more depolarized potentials, thereby activating more of the current in the diastolic range. This shift also speeds the rate of activation (34). Acetylcholine has different effects on i_f, depending on the species and also on the location in the heart. In sinus node i_f is shifted in the negative direction on the voltage axis, which reduces i_f activation and the amount of inward current it contributes. This effect appears mediated by GTP regulatory proteins (35). In sheep and rabbit Purkinje fibers acetylcholine accelerates the decay of i_f and accelerates diastolic depolarization (37, 38).

Recent reports suggest that alinidine can suppress pacemaker activity by acting directly on i_f (39). Alinidine appears to shift the i_f activation curve in the negative direction on the voltage axis, thereby reducing activation of the pacemaker current at any potential.

The relative contributions of i_f to the pacemaker potential of Purkinje fibers and the sinus node might provide an ideal locus for selective actions of antiarrhythmic drugs. Selective blockade of i_f could eliminate ectopic foci in the Purkinje system due to enhanced normal automaticity with smaller effects

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on the primary pacemaker. This effect would prove detrimental by causing ventricular standstill in those individuals relying on ventricular escape rhythms. A drug that selectively blocked i_f would prove invaluable as an investigative and diagnostic tool. However, even if a highly selective blocker of i_f could have appreciable use as an antiarrhythmic drug, there are additional concerns. The distribution of an i_f-like current in spinal sensory neurones (40), retinal rods (41), hippocampus (42), and smooth muscle cells (43) suggests that a wide array of side effects concomitant with drug administration may occur.

The Background K Current i_{K1}

The i_{K1} current is the major potassium conductance during diastole and is the major reason why the maximum diastolic potential approaches the potassium equilibrium potential, E_K (44, 45). Until recently it was thought that the inward rectifying property of this channel was instantaneous (46–48). We now know that this channel is gated by voltage and external K (half activated roughly 5 mV negative to E_K; open probability increases with increasingly negative membrane potentials). Positive to E_K, the conductance is also voltage-gated, and decreases in open probability *e*-fold per 5 mV depolarization (48, 49). The open channel conductance increases in proportion to the square root of $[K^+]_o$ (47). Internal Mg^{2+} has been shown to block i_{K1} at potentials positive to E_K (50, 51). The contribution of internal Mg^{2+} to inward rectification remains to be determined, since the open channel does not appear to rectify nearly as much when $[K^+]_o$ approaches physiologic levels (52, 53).

For whatever reasons, the i_{K1} conductance in the steady state is large negative to E_K, smaller about 10 mV positive to E_K, and negligible at potentials more than 40 mV positive to E_K. Thus, this conductance contributes negligible repolarizing current in the plateau range of potentials while contributing significant outward current during diastole (45).

The voltage-dependent activation of i_{K1} is rapid, with a tau_{activ} of 1–20 msec at 10°C, and should be virtually complete in 1–2 msec at physiologic temperatures (48, 49). At first glance, this suggests that time dependence of i_{K1} may be so rapid as to be irrelevant to physiologic and pathologic conditions. Such is not the case. Although the kinetics and voltage range of i_{K1} are probably irrelevant for the action potential plateau, the threshold for initiating sodium channel dependent action potentials occurs in a range where i_{K1} is present. Further, the rapid kinetics of Na^+ channel activation may approach the speed of i_{K1} deactivation. As a consequence, i_{K1} may particularly affect the upstroke of depressed, fast response-type action potentials. Studies of the kinetics of i_{K1} may lead to important insights into abnormal impulse initiation and conduction, and, conversely, the pharmacologic alteration of i_{K1} kinetics could be a useful approach to modifying these impulses.

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Additional time-dependence may be conferred on i_{K1} by K^+ fluctuations in narrow extracellular clefts because of at least two effects. First, since g_{K1} also has a K_o^+-dependent component, a decrease in cleft $[K^+]$ with time following an action potential will decrease the channel conductance. Furthermore, decreasing $[K^+]_0$ shifts the activation curve for i_{K1} in the negative direction on the voltage axis, thereby decreasing open probability. These two factors reduce g_{K1}, while the increase in driving force tends to increase i_{K1}. The resultant time-dependent fluctuations in $[K^+]_o$ create the impression of a much slower time-dependent i_{K1} whose time course is controlled by factors determining cleft K^+ decay [cleft dimensions, active transport, passive K^+ permeability (see 11)].

Agents that block i_{K1} decrease the maximum diastolic potential and increase the slope of the pacemaker potential, thereby increasing the frequency of spontaneous activity. Most divalent ions (such as Ba^{2+}, Sr^{2+}) may block i_{K1} to some degree, often in a voltage-dependent manner; blockade increases with increasing hyperpolarization (22, 54). Many monovalent cations also block i_{K1}, including Cs^+ and Rb^+ (31, 55). Conversely, Tl^+ is more permeant than K^+ (56).

With the knowledge that i_{K1} is voltage-gated, is present in subsidiary pacemakers (22), and is largely absent from the sinus node (57) comes the opportunity for selective pharmacologic action. Under conditions of ischemia and infarction, partial depolarization occurs which affects conduction and excitability (see 58–60). The membrane potential depends on g_K, which in turn depends on the open probability of i_{K1}. Under such circumstances it might be possible to develop a surface charge agent capable of shifting the activation curve for i_{K1} in a depolarized direction on the voltage axis. This action would increase the number of open i_{K1} channels for any given potential, causing a partial restoration of membrane potential. This same intervention could also diminish any "enhanced normal automaticity" present, with little or no effect on the primary pacemaker, the sinoatrial node.

Simulation

The computer simulation of the pacemaker potential was generated from the equations provided by McAllister et al (61) as modified by Cohen et al (62). (Although i_{K2} was employed, substitution of the i_f formalism should not alter the conclusions.) Not all background inward current during diastole flows through TTX-insensitive channels. An appreciable "window" current would be expected to contribute to the pacemaker potential, especially during late diastole. The magnitude of this current during slow diastolic depolarization is determined as follows:

$$I_{Na,\infty} = \bar{g}_{Na} \cdot m^3{}_\infty \cdot h_\infty \cdot (V\text{-}V_{Na})$$

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where m is the activation gating variable for the sodium channel, h is the inactivation gating invariable, $\bar{g}_{Na}$ is the sodium conductance when all sodium channels are open, and V_{Na} is the equilibrium potential for sodium ions. (The assumed kinetics for m and h are used for consistency with previous work and should not qualitatively determine the result.) The slowly inactivating sodium current would not be expected to directly participate in pacemaker activity, since it apparently deactivates very rapidly at diastolic potentials (G. A. Gintant and I. S. Cohen, unpublished observations).

Figure 1*a* shows the value of $i_{Na,\infty}$ for the control case as well as for a reduction in $\bar{g}_{Na}$ by 25 or 50%. Figure 1*b* illustrates the effects of shifts in h_∞

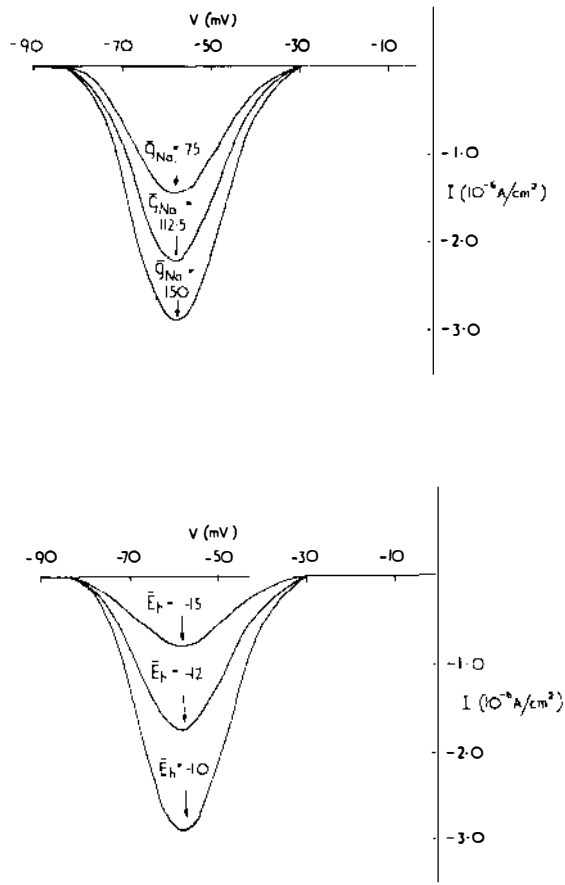

Figure 1 (a) A plot of steady state Na^+ "window" current (I) versus potential (V) for $\bar{g}_{Na} = 75$, 112.5, and 150 mS/cm^2. The equations for m_∞ and h_∞ are presented by Reference (57). (b) A plot of steady state Na^+ "window" current versus potential for $\bar{g}_{Na} = 150$ mS/cm^2 and α_h and β_h as given in Reference (62). Control ($\bar{E}_h = -10$); 2-mV negative shift of α_h and β_h ($\bar{E}_h = -12$); 5-mV negative shift of α_h and β_h and thus h_∞ ($\bar{E}_h = -15$).

of −2 and −5 mV on the voltage axis on the window current. Under control conditions there are about 3 μAmps/cm^2 of current flowing through the sodium window at −60 mV. At −80 and −30 mV less than 0.05 μAmps/cm^2 flows through these same channels. Thus the effects of the reduction of $i_{Na,\infty}$ (by reducing $\bar{g}_{Na}$ or shifting h_∞) should only be apparent during diastole at potentials positive to −80 mV. Of course, these effects depend upon an accurate mathematical representation of sodium channel gating and may be modulated by drug-induced changes in the action potential duration.

Figure 2*a* shows the effects of a reduced $\bar{g}_{Na}$ on the pacemaker activity of

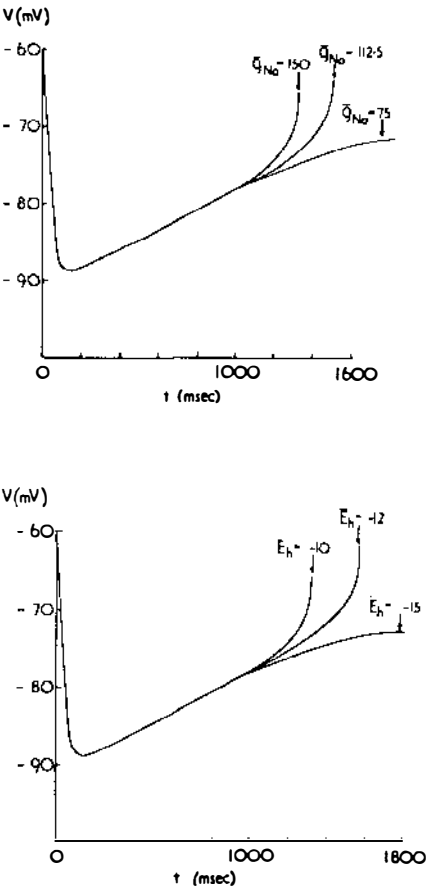

Figure 2 (a)A simulation of diastolic depolarization for the Purkinje fiber [with equations described in (61) and (62)] for $\bar{g}_{Na}$ of 150 mS/cm^2, 112.5 mS/cm^2, and 75 mS/cm^2. The diastolic interval was measured between the start of the simulation at −60 mV and when the pacemaker depolarization again reached −60 mV. (b) A simulation of diastolic depolarization with the normal h_∞ curve ($\bar{E}_h = -10$), and following a 2 mV shift in h_{inf} ($\bar{E}_h = -12$), and a 5 mV shift in h_∞ ($\bar{E}_h = -15$). $\bar{g}_{Na}$ = 150 mS/cm^2. Diastolic interval measured as in 2a.

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the Purkinje fiber. The diastolic interval is prolonged from 1320 to 1500 milliseconds when the sodium conductance is reduced to 75% of control. Further reduction of $\bar{g}_{Na}$ to 50% eliminated the regenerative response. Similar results were obtained when h_∞ was shifted in a negative direction on the voltage axis (Figure 2*b*): A 2-mV shift prolonged the diastolic interval from 1320 to 1560 milliseconds, whereas a 5-mV shift eliminated the regenerative response.

Most local anesthetic-type antiarrhythmic agents [Class 1 (see 63, 64)] reduce $\bar{g}_{Na}$ and effect a negative shift of the h_∞ curve on the voltage axis. The computer simulations above suggest that these agents should (*a*) reduce the slope of diastolic depolarization positive to −80 mV (in this model case or where $m^3{}_\infty h_\infty$ is nonzero in the general case), (*b*) cause a positive shift in the threshold potential for regenerative responses, and (*c*) reduce a window of inward current in the steady state current-voltage relation between −30 and −80 mV. These effects on late diastolic depolarization have been observed experimentally with the specific sodium channel blocker tetrodotoxin (65; G. A. Gintant, unpublished observations, but see 1, 66). In the case of diastolic depolarization in partially depolarized fibers, local anesthetic-type agents could have a more profound effect on diastolic depolarization owing to the larger depolarizing "window current" present along with the amount of inactivation already reducing the regenerative inward sodium current. The situation is complex, since reducing plateau sodium currents may also affect diastolic depolarization secondarily to changes in the action potential configuration.

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ABNORMAL AUTOMATICITY: TRIGGERED ACTIVITY AND AFTERDEPOLARIZATIONS

A type of abnormal automaticity implicated in arrhythmogenesis is that of triggered activity (see 67, 68). Triggered activity is induced by phasic afterdepolarizations that attain threshold to initiate nondriven action potentials. Afterdepolarizations are categorized by the relationship between the phasic depolarization and the action potential from which they derive: early afterdepolarizations (EADs) occur during phase 2 or 3 of the action potential (i.e. prior to full repolarization, hence the adjective early), whereas delayed afterdepolarizations (DADs) occur soon after action potential repolarization. With either form of afterdepolarization, sustained activity may result if the afterdepolarization reaches threshold to trigger a second (or additional) nondriven impulse.

Delayed Afterdepolarizations

In general, any intervention or abnormality that increases intracellular Ca^{2+} activity above a certain value may cause DADs. Experimental interventions

known to induce DADs include cardiac glycosides, elevated $Ca^{2+}{}_o$ (69–72, 145), and increased intracellular $[Na^+]$ or decreased $[K^+]_o$ (73, 74). DADs have also been observed in diseased tissues (75) and in Purkinje fibers surviving infarction (76–78).

Briefly, the mechanism by which cardiac glycoside intoxication leads to DADs is as follows (see also 79, 80). Cardiac glycosides bind to an external site of the activated form of the Na^+/K^+ ATPase (sodium pump) and reduce its activity. Since the inward background current is unaltered, an increase in intracellular sodium ensues, reducing the inwardly-directed Na gradient. The reduced gradient causes a secondary decrease in Ca extrusion via Na/Ca exchange (81–85), leading to an elevation of intracellular Ca^{2+} levels. The increase in $Ca^{2+}{}_i$ is thought to "overload" the sequestration mechanisms for Ca^{2+} storage in the sarcoplasmic reticulum (SR). Under normal conditions, an increase in $Ca^{2+}{}_i$ derived from transarcolemmal Ca^{2+} current during an action potential causes Ca-induced Ca^{2+} release from the SR (86). The SR then resequesters the Ca [via a Ca-stimulated ATPase (see 87)] to terminate the contraction. When a cell is in a calcium-overloaded state, these fluctuations increase in size (88–91). Each oscillatory release and reuptake generally induces (*a*) an aftercontraction (see 72) and (*b*) a conductance change in the cell membrane responsible for an inward current. This novel inward current, termed the transient inward (TI) current (92), is believed to be responsible for the DAD (93).

The nature of the glycoside-induced TI current is still debated. Reversal potential determinations suggest it is carried predominantly by Na^+ with some contribution of K^+ ions (93). This current may result from a Ca-activated nonspecific cationic conductance similar to one found in cultured neonatal rat hearts (94). A second possibility is that of electrogenic Na/Ca exchange. Recent evidence obtained from guinea pig atrial cardioballs suggest that both Na-Ca exchange current and a Ca-gated channel could contribute (85). Evidence from K^+-sensitive microelectrodes positioned within clefts suggests that either little K^+ flows during the TI current or else TI channels are activated in a nonhomogenous fashion (95, 96). A determination of the membrane system(s) responsible for the TI current will provide another focus for antiarrhythmic drug research and future diagnostic capabilities.

It is generally assumed that DADs and triggered activity induced by glycoside-intoxication and by other interventions are caused by the same mechanisms described above. However, DADs from different preparations and experimental conditions need not demonstrate similar characteristics. In canine Purkinje fibers, digitalis-induced DADs display a complex relationship between the stimulation rate, DAD amplitude, and the coupling interval between the triggering action potential and the DAD (see 97). Upon termination of a stimulus train with a basic cycle length (BCL) $>$ 500 msec, the first DAD is larger than subsequent "dampened" DADs. For BCL $<$ 500 msec, the

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second DAD usually is largest, with subsequent DADs displaying diminishing amplitudes. At shorter cycle lengths, DADs occur at shorter coupling intervals (70, 98). If triggering occurs, some depolarization of the maximum diastolic potential (MDP) may follow. Triggering may terminate suddenly, without any further change in MDP. Different results are obtained with canine coronary sinus preparations exposed to catecholamines (96, 98, 99): usually one DAD progressively increases in amplitude as the BCL decreases. If triggering ensues, it is often followed by a depolarization of the MDP with a gradual acceleration of rate; subsequently, hyperpolarization occurs and there is a gradual slowing of rate prior to termination of the triggered rhythm. The differing results obtained in these two preparations may be attributed (at least in part) to differences in extracellular K^+ accumulation and Na^+/K^+ pump activation in the two experimental conditions (96, 99). Further, such differing characteristics suggest that triggered activity in general may not be identified by any uniform set of guidelines (100).

Other factors that may modulate DADs include differences in SR function from different locations within the heart, as well as age and species differences (101). The level of free Ca^{2+} that induces Ca-release also varies, as may the amount of transmembrane Ca influx and resting $[Ca^{2+}]_i$. Little is known of the factors that modulate DADs in diseased tissues.

Given the complex scheme for the generation of DADs, it is not surprising that any number of experimental interventions can either directly or indirectly alter or minimize their appearance. A pharmacological approach can occur at many levels. We shall consider just a few possibilities. Ryanodine is an agent that blocks Ca^{2+} release from the SR in cardiac muscle (102–104) and may induce a Ca^{2+} leak from the SR (105) to deplete sequestered Ca^{2+}. Both actions may suppress both the frequency and amplitude of myocardial calcium oscillations. Ryanodine, in low concentrations, also abolishes digitalis-induced DADs (106, 107). Direct clinical applications for a ryanodine-like antiarrhythmic agent would have to contend with interference of excitation-contraction coupling of skeletal and cardiac muscle. More likely approaches would include a reduction of $[Ca^{2+}]_i$, possibly via calcium current blockade, or an enhancement of Na/Ca exchange, via lowering $[Na^+]_i$. Local anesthetic-type agents may do the latter and may prevent DADs through changes in action potential configuration. They may also prevent triggering by their effects on threshold potential. DADs that do not attain threshold to initiate triggering may yet be responsible for driven beats by enhancing excitability (108, 109). The involvement of DADs in arrhythmogenesis has been discussed elsewhere (110–113).

Early Afterdepolarizations

A number of experimental models have been used to characterize the behavior and mechanisms responsible for early afterdepolarizations (EADs), including

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exposure to excessive concentrations of catecholamines (114), quinidine (115), cesium (111, 116, 117), aconitine (118), reduced pH (119), N-acetylprocainamide (120), and amiloride (121). Early afterdepolarizations have also been observed in diseased tissues (75). If one considers the fine balance of currents flowing during the high-resistance plateau phase of the action potential, the number of interventions that lead to EADs is not surprising. The relevance of the above models to EADs and triggered automaticity observed in diseased or damaged myocardium is uncertain.

It has been suggested that there are at least two subtypes of EADs, based on their location within the action potential (67, 117). The first type, termed low membrane potential EADs, are found during the mid to later portion of the plateau (phase 2), generally at potentials ranging from 0 to −30 mV. The second type, termed high membrane potential EADs, occur just prior to completion of full repolarization (during phase 3), generally at membrane potentials more negative than −50 mV. To complicate matters, both types may be found in the same tissue and action potential. The currents involved in the genesis of each are likely different in type and magnitude, owing to the different voltage ranges over which each subtype evolves. This may lead to a pharmacological dissection of the two subtypes. Any relationships between the mechanisms responsible for EADs and depolarization-induced automaticity [DIA (122–124)] remain to be defined.

Although it is obvious that net inward current is obligatory for EAD generation, it is not obvious whether an increasing inward or a decreasing outward current initiates EADs. Between these choices, a de novo increasing inward current activated late during the action potential plateau would be a novel finding: A decreasing outward current(s) overlaying a background inward current would appear more likely. Furthermore, the process(es) responsible for continuing an EAD beyond "threshold" may be different from those initiating the EAD. Many studies aimed at elucidating the ionic mechanisms responsible for EADs fail to distinguish whether experimental interventions affect the processes of initiation or maintenance (or both). Action potential studies may be particularly misleading, since experimental interventions may change the early configuration of action potentials and thereby modify EADs.

For the remainder of the discussion, we shall focus primarily on the ionic mechanism responsible for EADs induced by cesium (Cs) and quinidine. Our understanding of quinidine-induced EADs is particularly important clinically because of the link of this commonly used drug to bradycardia-dependent triggered activity and tachyarrhythmias, including the potentially lethal arrhythmia Torsades de Pointes (see 125). We limit our remarks on quinidine to its effect on membrane channels, although we recognize that quinidine acts on numerous subcellular components that may play as yet unknown roles in the genesis of EADs.

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A number of inward currents have been implicated in the genesis of EADs. EADs induced by quinidine or Cs (which can be either high or low membrane potential type) are abolished by the sodium channel blockers tetrodotoxin and lidocaine (115, 116). This effect is presumably due to a reduction of the steady-state "window" current as well as to the slowly inactivating sodium current (see above). In the case of high membrane potential EADs, a local anesthetic would affect EADs by reducing the fast inward current of the upstroke. The role of TTX-insensitive inward background currents remains unclear.

The extent of involvement of calcium currents in the genesis of EADs is likely dependent on the type of EAD. One might expect the involvement of the L (longer-lasting) calcium current in low membrane potential EADs, and possibly both T (transient) and L calcium currents in high membrane potential EADs (see 126–128, also 129 for a review). Effects of classic calcium current blockers on EADs may be mininal or profound and may be related to the type of EAD as well as to nonspecific drug effects (119, 130). External Mg^{2+} also blocks EADs and triggered activity (131), an effect possibly related to its depressant effect on calcium-dependent action potentials (132) and calcium current (133). It is not known to what extent a slowly inactivating or calcium "window" current may be involved. Our ability to discern the involvement of electrogenic Na/Ca exchange current is hampered by the lack of a specific blocker.

The fact that EADs appear to follow changes in calcium current suggests that the initiating mechanism for EADs is similar to DADs, i.e., requiring Ca^{2+} overload and internal Ca^{2+} cycling. This is not true for Cs-treated ferret ventricular muscle, since these EADs are not diminished by ryanodine or intracellular Ca chelators and are not related to aftercontractions (107).

A number of outward currents have been implicated in the genesis of EADs. Computer simulations suggest that alterations of the inward rectifier current i_{K1} along with a simultaneous increase in sodium "window" current is required to elicit high membrane potential EADs (134). Cs has been shown to block i_{K1} (55, 135). Based on the expected role of i_{K1} in the terminal phase of repolarization (see above), one might expect blockade of this current to be associated with high membrane potential EADs, which has been reported (116, 117). One would also expect that a reduction in the delayed rectifier would promote EADs. Consistent with this expectation, quinidine has been shown to block i_K (8, 136, 137) and possibly alter its kinetics (138). However, the situation may be more complex, since tetraethylammonium [a known blocker of the delayed rectifier in neuronal preparations (139–142)] produces Purkinje fiber action potentials as long as 5 sec without causing EADs (143, 144).

It has been shown that EADs induced by Cs or quinidine are reversibly enhanced by moderately low $[K^+]_o$ (115, 117, 125). This effect may be

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attributed to the rectifying characteristics of the delayed rectifier i_K and inward rectifier i_{K1}. Electrogenic Na^+ "pump" current may also be reduced if $[K^+]_o$ is sufficiently lowered below 2 mM, thereby reducing outward current (146, 147). Both effects could shift net current sufficiently inward to facilitate EAD generation.

In general, EADs are more likely at low stimulation rates (this being in contradistinction to typical DAD characteristics). Although the Purkinje fiber action potential is prolonged at slower stimulation rates (due to a net decrease in outward current), this prolongation normally does not give rise to EADs. Any number of explanations can qualitatively account for the frequency-dependence of quinidine-induced EADs. For example, a quinidine-induced (time-independent) reduction of i_K, coupled with an already decreased outward current at plateau potentials, could facilitate EADs if sufficient and timely net inward current were present.

The situation is potentially more complex in that blockade of i_K by quinidine may be time-, voltage-, and concentration-dependent. Consider first the possibility that block of i_K channels may be voltage-dependent, with quinidine preferentially blocking K channels at negative (compared to positive) membrane potentials (see 136). Following an abrupt decrease in heart rate, the cell experiences a longer diastolic period. If block is voltage-dependent, this longer diastolic interval should result in more block (and less outward current) during the subsequent action potential. This action, coupled with an appropriate inward current, could promote EADs and triggered activity at slower stimulation rates. As a matter of comparison, block of delayed rectifier in squid giant axon by 4-AP is reduced by depolarization, whereas TEA block is enhanced by similar voltage protocols (148).

Consider the additional possibility that blockade of i_K by quinidine may be time dependent (see 149). Following an abrupt decrease in heart rate, the action potential grows progressively longer until a new steady state is attained. Borrowing from the modulated receptor hypothesis (150, 151), assume that i_K channels (which do not inactivate) are either in a resting or an open state (each with a characteristic K_d for drug binding) and that the open state channel binds drug more avidly. Assume further that a drug-bound channel is a blocked, nonconducting channel. With action potential prolongation at slower stimulation rates, the ensemble of i_K channels could, on average, be open longer and favor drug binding and channel block. Indeed, with the appropriate kinetics, block may increase significantly during a prolonged action potential. This time-dependent decrease in outward current could be the initiating event that leads the membrane to the threshold for an EAD at slow heart rates. Time-dependent block of delayed rectifier channels in neuronal preparations has been observed with numerous agents (139, 140, 148, 152).

Blockade of i_K by quinidine that can be either time- and/or voltage-de-

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pendent may usefully be considered as "reverse" use-dependent block of i_K channels, in the sense that more channels are blocked at slower stimulation rates. The concept of "reverse" use-dependent blockade of potassium channels is particularly relevant when considering bradycardia-dependent arrhythmias and Class III antiarrhythmic agents (153) that prolong action potential duration and refractoriness. If drug-induced triggered activity is a possibility, it would hopefully occur outside of the range of physiologic heart rates. Knowledge of a drug's potassium channel blocking characteristics would prove helpful in determining its arrhythmogenic and antiarrhythmic properties.

CONCLUSION

With our increasing abilities to study cardiac membrane currents in a quantitative manner have come new descriptions of the currents that contribute to the pacemaker potential and action potential plateau. In diastolic range of potentials the inward rectifier, i_{K1}, has now been shown to be a voltage-sensitive, time-dependent current. A new channel, i_f, has been discovered, whose selectivity and gating properties differ from those of channels previously thought to exist in the heart. At plateau potentials, a slow component of sodium channel inactivation and a steady state sodium "window" current have been demonstrated. Computer simulations and experimental results suggest that the "window" current also contributes to diastolic depolarization.

These new insights in cellular electrophysiology allow a more detailed description of the basis of arrhythmogenic phenomena like early- and delayed-afterdepolarizations. Further, they offer new hope for the development of novel antiarrhythmic agents. The exploration of the characteristics and heterogeneity of channel types within the heart, their modulation by disease, and possible functional relationships to subcellular components should continue to occupy our investigative efforts over the next decade and beyond.

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