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ANTIARRHYTHMIC AGENTS: THE MODULATED RECEPTOR MECHANISM OF ACTION OF SODIUM AND CALCIUM CHANNEL-BLOCKING DRUGS

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INTRODUCTION

At the time of the last review of antiarrhythmic drugs in this series in 1975 (1), the important developments in the field centered around the "classical" agents: lidocaine, procainamide, quinidine, diphenylhydantoin (now phenytoin), and propranolol. That review properly emphasized the importance of new information regarding the effects of these agents on diseased tissue (e.g. obtained from infarcted hearts) or on normal tissue stressed in the muscle chamber (e.g. by depolarization with potassium). However, data and concepts available at that time were not sufficient to explain the important differences among the effects of these drugs on different types of cardiac tissue, or the difference in sensitivity of diseased and depolarized tissue as compared to normal tissue.

Since 1975, a modest revolution in antiarrhythmic drug development, research, and clinical application has occurred. The number of agents in active clinical use or investigation in the U.S. is now more than 18 (2, 3). In addition, a major new class of agents, the calcium channel blockers, has come into general use (4, 5). Furthermore, an attempt has been made to extend our understanding of the mechanism of action at the molecular level: the modulated receptor hypothesis (6, 7).

This review concentrates on the antiarrhythmic drug literature pertinent to an evaluation of the modulated receptor hypothesis. A number of general reviews

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of the antiarrhythmic drug group have appeared in recent years (2, 8–14). In addition, numerous reviews and symposia have been published dealing with the calcium channel blocking agents (15–26).

MODULATED RECEPTOR HYPOTHESIS

The first crucial observation that led to the modulated receptor hypothesis for antiarrhythmic drug action was made by Weidmann in 1955 (Figure 1A). He observed that in the presence of cocaine, quinidine, procainamide, or diphenhydramine, cardiac sodium channels behave as if the voltage dependence of inactivation is shifted to more negative potentials (27).

A second milestone in the development of modulated receptor theory was the observation by Johnson & McKinnon in 1957 (Figure 1B) that the effect of quinidine upon $\dot{V}_{max}$ (maximum upstroke velocity) progressively increases with each successive action potential in a train (28), and the steady-state effect increases with increasing driving rate (Figure 1B). Furthermore, Heistracher showed that the reduction of $\dot{V}_{max}$ recovers exponentially between trains (29).

Thirdly, Chen et al (Figure 1C) showed that during diastole, use-dependent depression of $\dot{V}_{max}$ recovers slowly at depolarized potentials and more rapidly at more negative potentials (30).

These three observations have been confirmed for many of the sodium channel blocking antiarrhythmic drugs (see section on sodium channel blockers below) and for calcium channel blockers in cardiac tissue (see section on calcium channel blockade below) as well.

On the basis of these three key observations, and important studies in nerve (31, 32), it was concluded that the interactions of antiarrhythmic drugs with the cardiac sodium channel must be time and voltage dependent. One formulation of this notion is shown in Figure 1D. Specifically, the modulated receptor hypothesis (6, 7) postulates that (*a*) antiarrhythmic drugs bind to a receptor site on or very close to the transmembrane ionic channel; (*b*) the affinity of the receptor for the drug is modulated by the channel state and/or potential: rested (R), activated (A), and inactivated (I) channels (33) can have different kinetics of interaction with antiarrhythmic drugs; (*c*) drug-associated channels differ from drug-free channels in that they do not conduct and their voltage dependence is shifted to more negative potentials.

These modulated receptor postulates were expressed in a set of differential equations to obtain quantitatively testable predictions of drug action (7). Using a least square error search, we estimated the drug-receptor rate constants for quinidine and lidocaine (7). Although these rate constant estimates were based upon data from several laboratories, using various preparations and differing experimental conditions, they nevertheless were capable of satisfactorily predicting the effects of quinidine and lidocaine when used subsequently for data

over a range of driving rates, recovery intervals, and holding potentials that had not previously been tested (34). At the time the literature search for the present review was completed, more than 100 studies had referred to the modulated receptor hypothesis to describe the action of ionic channel blockers. In the sections below we shall review the evidence for the hypothesis and call attention to some unanswered questions that require further research.

SODIUM CHANNEL BLOCKERS

Use-Dependent Block

Unless a sodium channel blocker has exactly the same affinity for rested, activated, and inactivated channels and does not alter the voltage and time dependence of gating when bound to the channel, its action on the sodium current will be use-dependent under appropriate conditions. Indeed, clinically useful antiarrhythmic drugs have a low affinity for rested channels and a high affinity for activated or inactivated channels. As a result, some block develops with each action potential, and recovery from block occurs during rest. Use-dependent block will occur whenever the rest interval is too short for complete recovery from block. It is thus not surprising that all sodium channel blockers studied so far have been found to cause use-dependent reduction of, and slowed rest-dependent recovery of, I_{Na}, $\dot{V}_{max}$, excitability, or conduction (Table 1). A few reports have appeared that suggest the absence of use-dependent block of sodium channel blocking drugs (91–94). However, in each of these, the apparent lack of use-dependent block can be explained by the experimental protocol used. Thus, a driving rate of 1 Hz at normal resting potential as used by Singh & Vaughan Williams (94) is too slow to observe marked use-dependent block in the presence of amiodarone, because at this membrane potential recovery from block proceeds so quickly that little block remains at the time of the next beat. As a result, Singh & Vaughan Williams observed only a small (but significant) reduction of $\dot{V}_{max}$. The use-dependent reduction of $\dot{V}_{max}$ by amiodarone becomes much more marked when the preparation is either depolarized (causing slower recovery from block) or driven at faster rates (providing more time for block to occur at depolarized potentials and less time for recovery between beats) (38). The latter observation is also supported by clinical findings: amiodarone usually has little effect upon ventricular conduction, but it may prolong pre-existing His-Purkinje delay (39) or induce tachycardia-dependent right bundle-branch block (95).

Lee et al (91) reported that therapeutic concentrations of lidocaine and quinidine substantially reduce the sodium current in a "tonic" fashion but cause very little use-dependent block. These authors used a holding membrane potential at which 70% of the channels in their preparation were inactivated.

Table 1 Evidence for modulated receptor interaction with sodium channel blocking drugs

Drug	References
Alprenolol	35–37
Amiodarone	38,39
Aprindine	40–46
Disopyramide	47–51
Droperidol	52
Encainide	50,51,53
Ethmozin	54
Flecainide	51,55,56
Imipramine	35,57,58
Lidocaine and derivatives	30,35,49,51,59–69
Lorcainide	51
Mexiletine	50,51,69,71–76
Phenytoin	62,77,78
Prenylamine	36,79
Procainamide	35,49,51,62,80
Propafenone	81–83
Propranolol	37,60,62,84,85
Quinidine	30,34,37,49,51,62,86–88
Tocainide	35,37,49,51,61
Miscellaneous ß blockers	70,89,90

Since lidocaine and quinidine cause more block at depolarized potentials, and recovery from block occurs very slowly, block would remain close to the maximum possible under these conditions. Only limited use-dependent block can occur when "tonic" block is so great. Bean et al (96) used preparations clamped to more negative holding potentials and showed that marked use-dependent block develops in the presence of lidocaine. Similar findings were reported for quinidine by Colatsky (97).

Benzocaine has also been reported to lack use-dependence (92, 93). Benzocaine has a very short recovery time constant from block: 105 msec at −95 mV, 27 msec at −120 mV (92). Consequently, unless the driving rate is rather fast, recovery from block will proceed to completion during diastole. In the studies by Sanchez-Chapula et al, the rest interval between clamp pulses was 500 msec, i.e. 4.7 times the time constant of recovery. Therefore, only about 1%

Figure 1 A: Antiarrhythmic drugs shift the $\dot{V}$max–mV curve to more negative potentials [to the right in this figure from (27)]. B: Antiarrhythmic drugs block in a use- or frequency-dependent fashion (28). C: Recovery from block is strongly voltage dependent (30). D: Modulated receptor schema: R = rested; A = activated or open; I = inactivated channels. R·D, A·D, and I·D represent the equivalent drug-associated channels. For more details see (6, 7).

use-dependent block would be predicted. In nerve, Schwarz et al (98) also failed to observe use-dependent block for benzocaine. It should be noted that, while they were driving the preparation at 5 Hz, the depolarizing pulse was only 1 msec in duration, leaving 199 msec available for recovery. In contrast, when stimulating at 10–100 Hz, use-dependent block was observed in the presence of benzocaine (99–102). In an unpublished study in cardiac tissue, we have found that the time constant of recovery from block by benzocaine can be lengthened by depolarization of myocardium. In guinea pig papillary muscle depolarized to −70 mV, benzocaine causes marked use-dependent block when stimulated at 5 Hz (Figure 2).

Thus, the evidence available so far is consistent with the claim that all sodium channel blockers exhibit use-dependent block under appropriate conditions, i.e. when "resting" block is maintained at a low level and diastolic interval is shorter than the recovery time.

Rested, Activated, and Inactivated Channel Blockade

Use-dependent block suggests different affinities for the individual channel states, i.e. state-dependent rate constants. (As noted below, an alternative or supplementary mechanism involves voltage-dependent rate constants of drug-receptor interaction. This mechanism is less well supported by the available evidence.) Although numerous investigators have discussed their results in terms of the modulated receptor hypothesis, only a few have estimated the affinities (or dissociation constants) for the individual states (see Table 2). In reviewing the literature we found two postulates that are consistently supported: (*a*) antiarrhythmic drugs have a low affinity for rested channels but a

Table 2 Dissociation constants for channel states and voltage shifts for several sodium channel blocking drugs

Drug	Kd_R (M)	Kd_A (μM)	Kd_I (μM)	V Shift (mV)	Method[a]	Reference
Amiodarone	0.1	1,000	20	50	G	38
Lidocaine	2.5	30	40	30	G	7
	2.5	92	37	25	G	61
	0.000 440	Large	10	19	NG	96
Mexiletine	∞		4		NG	71
Procainamide	1.85	37,000	370	50	G	80
Propafenone	0.3	1.0	0.5	55	G	103
Quinidine	∞	103	0	40	G	7
QX-314				30	NG	104

[a]G: global estimates of the four variables from experimental data; NG: non-global estimates from experimental data.

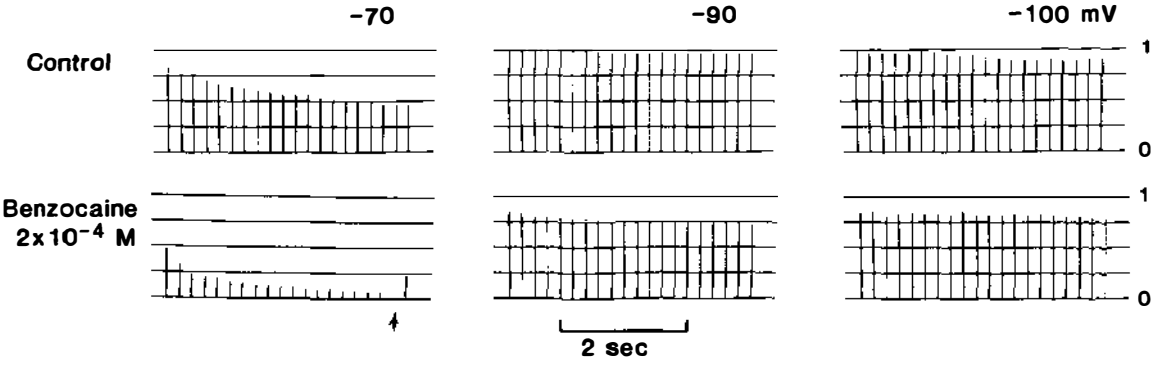

Figure 2 Use-dependent reduction of $\dot{V}$max by benzocaine (2×10^{-4}M) at 5 Hz. In each panel, normalized $\dot{V}$max for each action potential in a train of 20 are shown. Recovery from benzocaine block is so fast at −80 and −100 mV that little use-dependent block is observed. However, at −70 mV recovery is greatly slowed and use-dependent block becomes so marked that the preparation can no longer follow the stimulus train (see arrow). The resulting extra diastolic time provides for substantial recovery from block in the subsequent action potential.

relatively high affinity for the activated or inactivated channels or both; (*b*) unless the affinities for the three channel states are determined in a global fashion, the estimates for the affinity constant for any given state can be severely contaminated by the effects of the other states.

Open channel block may contaminate the estimates of the non-open state dissociation constants, because channel block can only be estimated by activating the channels. Therefore, block occurring during activation by the test pulse, but before the measured peak, will cause an overestimate of the actual block at the start of the test pulse. For example, a non-global estimate of rested block may underestimate the dissociation constant (overestimate rested affinity) by attributing open channel block to rested channel block. Quantitatively, approximately 10% of the total open channel time occurs before $\dot{V}_{max}$, and an even greater percentage before the peak of the sodium current. Any blockade of channels occurring during this time would be measured as apparent rested block. This effect can not be ignored, since studies in nerve have shown that open channels can have a high affinity for local anesthetics and that their blockade occurs with a time constant in the 100–1000 μsec range (105–111).

Inactivated state blockade may also contaminate non-global estimates of the affinity of rested or activated channels because many drugs have a very high affinity for the channel receptor in the inactivated state (i.e. a K_{d_I} in the μM range). To the extent that even a very small fraction of the drug-free channels are in the I state, a substantial fraction can nevertheless become trapped in the I·D (see Figure 1) state during rest (for the reason explained in Table 3). This

Table 3 Relation of inactivation voltage shift and rested state dissociation constant[a]

V-shift (mV)	K_{d_R} (M)
0	0.000 008 3
10	0.000 008 5
20	0.000 01
30	0.000 07
40	0.003 3
50	0.18
60	1.8

[a]The table shows the value of K_{d_R} (rested state dissociation constant) required if the first sodium current after an infinite rest period is to be reduced by 10%. Values were obtained using the modulated receptor equations (7) for a 1 μM drug concentration and resting potential of −90 mV. The affinities for activated and inactivated channels were set at zero. The voltage shift was varied from 0 to 60 mV. As the voltage shift is increased, the drug-associated channels behave as if they are more depolarized. This shifts the equilibrium between R.D. and I.D. (see Figure ID) toward the inactivated form, thus trapping progressively more channels in the I.D. pool. Consequently, to keep the total block less than 10%, the minimum rested state dissociation constant must progressively be increased, i.e. the affinity must be decreased.

also would appear as rested channel block. In cardiac tissue at room temperature, inactivation is substantially shifted to more negative potentials (92, 96, 112). Under these circumstances, rested block may be overestimated (91, 96) unless the holding potential is markedly hyperpolarized to remove all inactivation.

The voltage shift (discussed below) may also distort non-global estimates: it will translocate R·D channels to the I·D (see Figure 1) pool, again leading to an overestimate of the rested state affinity. A similar case can be made for distortion of the estimates for open or inactivated state affinities if non-global fitting is used. Because of these interactions, it is best to determine these affinities using a global least-square error search method (7).

RESTED BLOCK The literature cited in the first section shows that at normal resting potentials therapeutic concentrations of clinically useful antiarrhythmic drugs reduce the sodium current very little, if at all, when the channels are not used, i.e. when they remain in the rested state. Using the modulated receptor equations (7), one can compute the effect of antiarrhythmic drugs under rest conditions (i.e. "tonic" block). Table 3 shows the minimum possible rested state dissociation constants that will result in a low (less than 10%) block of rested channels. As explained in Table 3, this estimate is strongly dependent on the magnitude of the voltage shift of inactivation. Thus, the model predicts that for a drug with a typical voltage shift of about 40 mV, the K_{d_R} must exceed 3 mM if little or no resting block is to occur. Experimentally, it has been observed that at normal resting potentials, concentrations of sodium channel-blocking drugs near the mM range are required to observe "tonic" block in heart. Similarly, when studying local anesthetics in nerve, tonic block is usually observed only when mM drug concentrations are applied [tonic block is usually the variable measured; for reviews see (113, 114)]. In contrast, when studying the effects of therapeutic concentrations of antiarrhythmic drugs (μM range), there is usually little tonic block at normal resting potential. It is thus not surprising that the estimates of rested state dissociation constants determined by global fitting for the drugs in Table 2 are rather large ($K_{d_R} > 0.1M$). Since all of these global fits were obtained in μM drug concentrations, estimates of these large dissociation constants cannot be accurate. Nevertheless, they can be interpreted as showing that the rested channel affinity for these antiarrhythmic drugs is too low to be measured accurately at therapeutic drug concentrations.

As noted above, unless all the state-dependent dissociation constants are determined simultaneously, i.e. by a global fitting procedure, serious overestimates of the rested state affinity are probable. When contributions from activation and inactivation block are excluded, rested channel block by therapeutic concentrations of antiarrhythmic drugs is found to be negligible. In Hodgkin-Huxley terminology, this can be interpreted as indicating that occu-

pancy of the channel receptor by an antiarrhythmic drug is unlikely when the activation gate is closed and the inactivation gate is open. As a result, antiarrhythmic agents that can exit from closed channels (e.g. neutral lipophilic drugs) will do so.

ACTIVATED CHANNEL BLOCK VERSUS INACTIVATED CHANNEL BLOCK In nerve, open channel block was first convincingly demonstrated by Strichartz (31) for quaternary lidocaine derivatives. Lidocaine, quinidine, procainamide, and phenytoin have also been shown to block batrachotoxin-activated sodium channels (115). Hille (6) proposed that the channel receptor is accessible through a hydrophilic pathway from the inside of the cell when the channel is open. Since sodium channels in heart behave very much like those of nerve (7) and since at body pH antiarrhythmic drugs exist in the neutral and charged forms, it is conceivable that the charged form could similarly block open cardiac sodium channels. However, because the free-running cardiac action potential lasts so long, direct measurement of "pure" open channel block, i.e. with minimal contamination by inactivation block, can only be done by using the voltage clamp technique to impose short pulses. Some evidence is available for specific agents.

Quinidine Colatsky (97) showed that, in rabbit Purkinje fibers bathed in low sodium and at room temperature, the reduction in sodium current by quinidine (5 μg/ml) is mostly due to blockade of open channels. Moreover, lengthening of the pulses in the train from 50 to 5000 msec produced little additional block. This suggests that quinidine has a relatively low affinity for inactivated sodium channels. These observations are in agreement with earlier global estimates of the dissociation constants (7). In contrast, in ovine Purkinje fibers bathed in normal sodium and at body temperature, quinidine (10 μg/ml) caused a greater, but slowly developing (seconds), reduction of $\dot{V}_{max}$ as the pulse duration was increased (116). However, these authors also concluded that in therapeutic concentrations (< 2 μg/ml), inactivation block is less important and that the main mechanism of action of quinidine in reducing $\dot{V}_{max}$ must be block of open channels. We have also found that quinidine's block can increase with clamp duration in guinea pig papillary muscle (T. Matsubara et al, unpublished observation). However, the time constant of this slow phase of block (2–5 sec) is very similar to that of slow inactivation and has similar voltage dependence (117–118). This suggests that quinidine may promote slow inactivation. This voltage-dependent, slowly developing action of quinidine is different from all other drugs tested so far (see below): the block with other drugs develops much faster than with quinidine (hundreds of msecs instead of seconds; see below) and the extent and rate of inactivation block development is not strongly voltage dependent. To what extent "slow-inactivation block" by quinidine and

other antiarrhythmic drugs may constitute an important mechanism of antiarrhythmic drug action needs further investigation. Thus, for quinidine the order of affinity for the sodium channel states appears to be activated > inactivated >>> rested.

Lidocaine A global fit based on $\dot{V}_{max}$ data (7) suggested that lidocaine has about equal affinities for activated (K_{d_A} = 30 μM) and inactivated (K_{d_I} = 40 μM) channels. Bean et al (96) have shown that lidocaine has indeed a very high affinity for inactivated sodium channels (K_{d_I} = 10 μM). The time constant of inactivation block at room temperature was a few hundred msec for 20 μM lidocaine, but shortened to only 10 msec for 200 μM drug. According to the modulated receptor model, when all the channels are in the I and I·D pools (Figure 1), the time constant for inactivation block is: $1/(k_I[D] + l_I)$, which shows that increasing the dose ([D]) may reduce the time constant. Sanchez-Chapula et al (92) also observed a high affinity and similar time constants for inactivated channel block by lidocaine.

In contrast to our initial estimates for lidocaine, neither Bean et al (96) nor Sanchez-Chapula et al (92) observed much activation block. This is not surprising, however, given their experimental protocol. A cationic drug in a hydrophilic transmembrane channel is expected to distribute according to the Boltzmann equation. As a consequence, concentration at the receptor site, and the blockade, will be more marked the more depolarizing the pulse (within limits) and vice versa (31, 32, 119, 120). Yeh & Narahashi (105) and Cahalan (121) directly demonstrated this effect experimentally in nerve and showed that it is mostly the rate constant l_A that is voltage dependent. For pancuronium and 9-aminoacridine the dissociation rate constant, l_A, becomes progressively smaller at more positive potentials. As a result, open channel block sharply declines as the clamp potential is made more negative, so that at −30 mV, the usual potential for clamp pulses in both of the above cardiac studies (92, 96), one might expect little activated channel block (120). In fact, in the one experiment in which Bean et al clamped to more positive levels (+31 mV) (see their Figure 9A), they too observed activation block for lidocaine. With free-running action potentials the membrane potential reaches positive levels while a substantial fraction of the sodium channels are still open, so a greater degree of activated channel block is expected to occur (122). Thus, lidocaine's affinities for the individual channel states appear to be: inactivated ≥ activated >>> rested. The exact relation between the first two may be influenced by pH (as discussed below).

Other drugs Amiodarone (38) appears to cause little or no open channel block, since a fast train of 19 short pulses (5 msec at 3 Hz) results in no reduction of $\dot{V}_{max}$. In contrast, even a single long pulse (100–6000 msec) can

markedly reduce $\dot{V}_{max}$ of a test pulse. Similarly, Sada (80), using a global search, has shown that procainamide elicits much less open channel block than lidocaine. Hence, for amiodarone and procainamide, the channel affinities appear to be best represented as: inactivated >> activated >>> rested.

Disopyramide, although in many respects similar to quinidine (123), is probably more of an inactivation blocker. Indeed, the percentage blocking effect of this drug increases with depolarization (124). In addition, hyperpolarization by reduced external potassium can increase disopyramide's effect (48). This anomalous effect can occur with inactivation blockers that have a long time constant of recovery from block. This may be due to the fact that reduced external postassium can lengthen the action potential duration and consequently promote inactivation block; this extra block can be observed on the subsequent beat.

According to Courtney's analysis (71), mexiletine also has a substantial affinity for the inactivated state (K_{d_i} = 4 μM). His analysis did not provide an estimate for open channel block.

Voltage Dependence

Rested sodium channels have a much lower affinity for antiarrhythmic drugs than depolarized (activated or inactivated) channels. In addition, the rate of recovery (re) from block is slower (the time constant, τ_{re}, is larger) the more depolarized the holding potential (Table 4). According to the modulated receptor hypothesis, the rate of recovery from block should be voltage dependent along two separate routes: (*a*) the I·D to I to R, and (*b*) the I·D. to R·D to R pathways (Figure 1D).

THE I·D TO I TO R PATHWAY Since recovery from inactivation (I to R) is strongly voltage dependent (33, 127, 128), the recovery from block (I·D to I to

Table 4 Publications showing low drug-receptor affinity in rested channels and voltage dependence of recovery from block

Drug	References
Amiodarone	38
Benzocaine	92
Droperidol	52
Lidocaine	30,34,61,69,91,92,96,125,126
Mexiletine	73
Prenylamine	79
Procainamide	80
Quinidine	116
Tocainide	61

R) may, a priori, also be voltage dependent. However, the extent of the voltage dependence will appear very different for individual drugs. If the time constants of the I·D to I and I to R transitions are of the same order of magnitude, especially if $k_I > 0$ (e.g. lidocaine), the overall recovery process (I·D to I to R) will appear strongly voltage dependent. Indeed, from −85 to −70 mV, τ_{re} increased from about 200 to 500 msec (30, 61, 96). At more positive potentials, τ_{re} increases and, because of the high affinity of lidocaine for inactivated channels, most of the channels remain blocked. In contrast, when the time constant for the I·D to I process is much greater than that of the I to R transition, and especially if k_I is very small (e.g. quinidine), then after the initial fast recovery of the channels in the I pool the time constant of the global recovery process will approach $1/l_I$ (34, 116). Since the closed channel rate constants are not strongly voltage dependent (see below) the recovery will appear to be only slightly voltage dependent. In fact, over the −85 to −70 mV range, the τ_{re} for quinidine changes only from 5 to 7.5 sec (116).

THE I·D TO R·D TO R PATHWAY As the membrane potential is made more negative and the voltage shift of drug-associated channels is overcome, an additional path for recovery becomes available: I·D to R·D to R (see Figure 1D). This pathway appears to be very fast: Hondeghem & Katzung (34) found that in the −120 to −140 mV range of resting potentials, recovery from quinidine block occurs so rapidly that it is not possible to induce use-dependent block with a 3 Hz pulse train, even if the concentration is increased to 16 μg/ml. Therefore, it appears that for quinidine, the recovery process shifts from a relatively slow process (on the order of 5 seconds) to a much faster recovery process (less than 50 msec) around −120 mV.

For lidocaine, the potential at which the recovery kinetics shift from slow to fast is less negative, and use-dependent block at 3 Hz disappears around −105 mV (34). Similar results were obtained for phenytoin (129) and benzocaine (see Figure 2).

For amiodarone (38) and aprindine (129), the hyperpolarization must be to at least −140 mV to attenuate use-dependent block. Thus, the latter two drugs appear to have a voltage shift larger than that for quinidine, while the voltage shifts for lidocaine, phenytoin, and benzocaine are smaller.

A shift in the voltage dependence of inactivation of drug-associated channels was proposed quite early in studies of cardiac tissue (27) and nerve (32). Recently, Weld et al (116) have questioned the existence of the voltage shift. However, the apparent voltage shift of inactivation, i.e. that, measured experimentally, ranges from zero (when no channels are blocked), to the actual shift that would be observed when all the channels are blocked. Unfortunately, since blocked channels do not conduct, the actual voltage shift cannot be measured directly. Since Weld et al combined μM concentrations of quinidine

with slow driving rates, few channels would be blocked and, as expected, they observed only a small voltage shift (3 mV). Small concentrations of lidocaine also cause only a small apparent voltage shift [3.5 mV at 17 μM (30); 4.4 mV at 21 μM (69); 4.7 mV at 20 μM; and 5.8 mV at 40 μM (96)]. However, the shift increases as the dose is increased. Thus, at 1 mM lidocaine, Bean et al (96) observed a voltage shift of 22 mV in rabbit, and Payet et al (67), using 426 μM, measured a voltage shift of 40 ± 10 mV in rat. Although these direct experimental estimates may be somewhat contaminated by block occurring during the test pulse, the values are in fairly good agreement with estimates obtained from global fits: 25 mV (61) and 30 mV (7).

An important test of the voltage shift concept is the demonstration of open channel *unblocking*. The experiment requires that (*a*) a large fraction of channels be trapped in the drug-associated inactivated (I·D) pool; this is the normal consequence of rapid use-dependent blocking at normal or low resting potentials; and (*b*) a subsequent strong hyperpolarization be used to quickly translocate the blocked channels into the R·D pool. If an activation is then elicited so that the ratio of A·D channels to A channels exceeds the equilibrium ratio, one should observe activation unblocking. This was, in fact, demonstrated experimentally quite early by Strichartz (31) in nerve and by Gintant & Hoffman in cardiac fibers (130 and personal communication). In addition to demonstrating that a strong hyperpolarizing prepulse markedly enhances recovery from block, they showed that when the prepulse was within one millisecond of activation there was a substantial additional recovery from block. It is difficult to explain this result without invoking a voltage shift of inactivation and unblocking of the channel during the open state.

A second test of the voltage shift hypothesis is the prediction that the $\dot{V}_{max}$-V_m curve can exhibit a "bump," i.e. a double sigmoid contour (7) at certain rates in the presence of drugs. Such double-contoured $\dot{V}_{max}$-V_m curves have been reported (56, 131). This bump is most convincingly demonstrated with quaternary compounds. However, the presence of a bump is compatible with *either* a voltage shift *or* voltage-dependent drug rate constants (116). Both mechanisms are compatible with the modulated receptor hypothesis and predict a bump at appropriate driving rates. If the bump is such that at certain rates the $\dot{V}_{max}$-V_m curve shows a flat region (in the voltage range where all drug-free channels are fully recovered) between the two sigmoid regions, then this is easily explained by a *voltage shift*. The same characteristic would require an unusually complex *voltage dependence* of the rate constants.

It is quite possible that, in addition to a voltage shift, the drug binding and unbinding rate constants may also be voltage dependent. Thus, Starmer et al (132) have proposed a model that explicitly incorporates voltage-dependent rate constants. They assume that the drug is charged and consequently that its distribution in the sodium channel is governed by the Boltzmann equation, i.e.

is potential dependent. Such a proposal appears quite reasonable for the charged form of the drug interacting through the hydrophilic pathway (6) and has been demonstrated experimentally in nerve (105, 121). However, there is good evidence that the neutral form of the local anesthetics can also effectively block sodium channels (92, 93, also see Figure 2). As proposed by Hille (6), the uncharged molecule can move laterally through the lipid membrane to combine with the receptor in the inactivated channel. In this situation there is no reason to anticipate inactivated state block would be voltage (as opposed to state) dependent. In fact, it has been shown that block by amiodarone (38) and lidocaine (92, 96, 122) is mostly independent of voltage over a range of −40 to +40 mV, where channels are inactivated.

One experimental study noted above did report that the closed-state interactions (rested and inactivated) of quinidine are voltage dependent (116). However, the data analysis of that paper has been questioned (133). As noted above, the slow voltage-dependent block described (116) appears to have a voltage- and time-dependence similar to that of slow inactivation (117, 118).

In summary, the action of antiarrhythmic drugs is strongly voltage dependent for at least three reasons: (*a*) affinity of depolarized channels for antiarrhythmic drugs is much larger than that of rested channels; (*b*) recovery from block occurs much more slowly in inactived than in rested channels; (*c*) inactivation of drug-associated channels is shifted to more negative potentials. Whether the association or dissociation rate constants of rested and inactivated states are also voltage-dependent will require further studies.

pH Effects

Most antiarrhythmic drugs are weak bases, with pKa ranging from 7.5 to 9.5. Thus, at physiological pH these drugs exist in both the cationic and the neutral form in the ratio determined by the Henderson-Hasselbalch equation. Many investigators have observed that the action of local anesthetics is pH dependent. Both the neutral (134) and the cationic forms of these drugs (135–137) have been proposed to be the active species. Hille (6) has made a very convincing case for the proposal that both the neutral and cationic species are active. The cationic drug can access the receptor only from the inside of the membrane and only when the channel is open. The neutral drug can interact with the receptor even if the channel is closed, gaining access to it through the lipophilic membrane phase. These observations have been confirmed in heart by Gliklich & Hoffman (138), who showed that in cardiac tissue, as in nerve, quaternary lidocaine derivatives are most effective when applied internally.

Small changes in pH can markedly alter the ratio of neutral-to-charged drug species. This in turn can alter the drug's effectiveness in several ways. First, external acidosis promotes the cationic drug form. Since this species partitions less readily into membranes (139), it is expected that the onset of drug action

will be slowed (140). Furthermore, the equilibrium concentration in the membrane will be reduced under conditions of acidosis. Therefore, drugs that act primarily as blockers of the inactivated channel might have a reduced effect. On the other hand, acidosis may prolong the action potential, thereby providing a longer time for inactivation block to occur (141, 142). Since the concentration of neutral drug in the extracellular fluid is in equilibrium with the membrane concentration, external acidosis will, by translocation of drug from the sarcoplasmic pool to the extracellular pool, also reduce activation block (assuming the internal pH remains relatively unchanged) (143). Finally, external acidosis facilitates protonation of the receptor-bound drug (98, 144) and, since only neutral drug can dissociate from closed channels, recovery from block is expected to be slowed by acidosis. Indeed, Grant el al observed that when the extracellular pH was reduced from 7.4 to 6.9, the time constant of recovery from block was increased by 66% for quinidine (86) and over 100% for lidocaine (126). As a result, significant use-dependence occurs at slower heart rates. The net effect of acidosis will depend upon the relative importance of the reduction in block developed per action potential versus the increased persistence of block. Thus, Grant et al (86) observed little change in the potency of quinidine, whereas Nattel (144) found a small increase in potency. It therefore appears that for therapeutic concentrations of quinidine, the loss in activation block approximately balances the persistence of block at 1–2 Hz. In the case of lidocaine (which is also a potent inactivation blocker) block development may not be reduced much because of the lengthening of the action potential duration (141, 142). This together with the significant slowing of recovery can markedly potentiate the effect of lidocaine in acidosis (126, 144).

Usually, the intracellular pH is 0.2–0.3 units more acid than the external pH (145, 146). Since the neutral drug freely equilibrates across the cell membrane, one can calculate that the internal cationic concentration will be higher than the external. However, during cellular ischemia this pH gradient may be enhanced, resulting in a further relative increase of the cationic internal drug (147). Such an increase could markedly enhance activation block.

Finally, acidosis promotes the extrusion of intracellular potassium (148, 149). This may result in a marked increase of extracellular K^+, which in turn can produce substantial depolarization and enhance the voltage-dependent effect of antiarrhythmic drugs.

Conversely, alkalosis may tend to hyperpolarize the membrane potential and thereby reduce the effect of antiarrhythmic drugs. In addition, alkalosis promotes the neutral drug form, and recovery from block will occur more quickly (96). Alkalosis may also cause transient sequestration of drug from the aqueous phase into the lipid phase. For an activation blocker like quinidine, all these actions would be expected to reduce the effect. Alkalosis-inducing salts such as

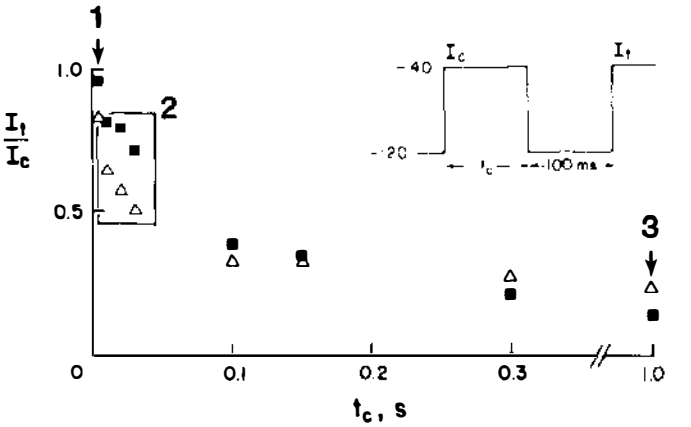

Figure 3 Effects of pH upon rate of development of block by lidocaine (200 μM) [Figure 10 from (96)]. Filled squares: pH = 7.0; open triangles: pH = 8.1. Alkalosis results in more activation block (1, arrow), faster development of inactivation block (2, box), and less steady-state block (3, arrow) (for explanation see text). Modified and reproduced from *The Journal of General Physiology* by copyright permission of The Rockefeller University Press and the authors.

sodium lactate have been traditionally used to combat toxicity caused by quinidine (150–151).

It should be noted, however, that under steady-state conditions external alkalosis will cause more neutral drug to dissolve in the membrane and thereby result in an increase in drug available for access to the inactivated channel receptor as well as an increase of internal drug concentration. As a result, activation block may actually become more marked and inactivation block may develop faster, but faster unblocking may result in less-steady–state block (see Figure 3).

Thus, the effects of pH can be quite complex. They will depend upon whether the change in pH is mostly intracellular or extracellular, whether the drug mostly blocks activated or inactivated channels, and the extent to which resting membrane potential and action potential duration are changed.

Structure-Activity Relationships

Traditional structure-activity analysis of local anesthetic (and antiarrhythmic) drugs have attempted to correlate physicochemical properties with a single "potency" figure. When block is measured in nerve by the usual techniques, the overall lipid solubility does correlate well with potency (113, 134, 135). However, the modulated receptor hypothesis predicts that a drug has three potencies, one for each of the channel states. Therefore, the reported single-

value potencies must be intermediate between the lowest and the highest of the three state potencies. It is not surprising, therefore, that individual drugs can be reported as having very different potencies, depending upon the tissues used (71) or the experimental conditions. For example, chlorprocaine has been reported to be equal in potency to procaine (152) or four times as potent (114). This type of discrepancy would be greatly diminished if potencies were reported for well-defined standard experimental conditions or, better, if the potencies for the individual channel states were reported.

Recently, Courtney has shown that at 3 Hz antiarrhythmic drugs within a structural series, e.g. amides, may show a strong correlation between lipid solubility and potency (153). Non-amides appear generally more potent. Since the membrane potential of the cardiac cells was not voltage clamped in these studies, the potency of the inactivation blockers might have been altered by changes in action-potential duration.

The rate of block development can be roughly predicted on the basis of ionic charge on the local anesthetic molecule: quaternary compounds block rather slowly (93), while neutral compounds block much more quickly (92). For tertiary compounds the rate of block development appears intermediate and can be altered appropriately by pH (98).

For recovery from block, one would expect that lipophilic drugs, which can freely diffuse through the membrane, would exhibit the fastest recovery-time constant. However, Courtney has shown that the time constant of recovery correlates much better with molecular size than with lipid solubility (35). Sada & Ban (90) similarly showed that in a series of β-blockers the recovery time constant was more closely related to molecular weight than to lipid solubility. It appears that molecular weight and lipid solubility together can account for a significant part of the structure activity relations (over 20 drugs were analyzed in the above references). However, there must also be other important components. Firstly, several drugs deviate significantly from Courtney's molecular weight-lipid solubility rule (56, 89, 154). Secondly, it is possible to make small changes in compounds that only minimally alter their physicochemical properties, but nevertheless dramatically alter their electrophysiological blocking properties (155–157). Thirdly, stereoisomers that have identical physicochemical properties can nevertheless have markedly differing blocking properties (158). Clearly, in addition to the molecular weight-lipid solubility rule there must exist some stereoselective interactions between the receptor and the drugs (153). Unfortunately, no studies have yet correlated the modulated receptor affinities with various physicochemical properties of the drugs. We hope that by the time the next review in this series appears, it will be possible to give a more detailed account of quantitative structure analysis in relation to the channel receptor states.

CALCIUM CHANNEL BLOCKADE

There is now ample evidence (see reviews cited in introduction) showing that members of the verapamil, diltiazem, and nifedipine drug groups, as well as several inorganic polyvalent cations, reversibly diminish ion flux through membrane calcium channels as their primary effect. For several reasons, analysis of the mechanisms of this action is less complete than that of the sodium channel-blocking agents. Chief among these reasons is the still incomplete picture of physiological gating in the calcium channel (159–161). Second, there appear to be great differences between calcium channels in various species, between channels in different tissues of a given species, and even between channels in a given tissue at different stages of development (160, 161). Third, calcium influx through the membrane channels is modulated in many tissues by a variety of chemical agents (161, 163). Nevertheless, the kinetics and voltage-dependence of the cardiac calcium channel can be described *operationally* using conventional Hodgkin-Huxley variables and three states (rested, active, and inactivated) in analogy with the sodium channel (162, 164–166). Furthermore, considerable evidence is already available that suggests that the receptor for at least some of the organic calcium channel blockers is modulated by channel state or voltage. The modulated receptor hypothesis for the action of calcium channel blockers has recently been extended to smooth muscle (17, 167, 168). The most convincing evidence for the modulated receptor mechanism in the cardiac calcium channel comes from direct voltage clamp measurements of the calcium current (I_{si}), but the argument is also strongly supported by a marked frequency dependence of the negative inotropic action of verapamil and its congeners and of the effects of members of the verapamil and diltiazem groups on action potentials.

Use-Dependence

The earliest evidence suggestive of use-dependent blockade by calcium channel blockers can be found in studies of slow responses (169) and contractility (170–174). The first definitive evidence of use-dependent block of I_{si} was published by Ehara & Kaufmann (175) in a study of verapamil. This work was followed by a detailed study of D600 by McDonald et al (176) that fully confirmed the use-dependence as well as other modulated receptor characteristics of block by the verapamil congener. Subsequent voltage clamp studies have shown that diltiazem (177–179) as well as verapamil and its congeners (178, 180, 181) have strongly use-dependent effects on I_{si} in cardiac muscle. More recent studies of slow responses and force of contraction are fully consistent with this interpretation for papaverine (182, 183) and other calcium channel blockers (184, 185).

Voltage-Dependence of Recovery

Ehara & Kaufmann (175) in their voltage clamp study of verapamil showed that use-dependent block could be markedly reduced by a holding potential of −120 mV compared to the normal holding potential of −80 mV. The fact that this modulation of block represents the voltage dependence of the recovery from block produced by the activating-inactivating pulse was well demonstrated for D600 by McDonald et al (176). Trautwein and coworkers (180, 186) showed that blockade by AQA39 and by D600 was similarly removed by hyperpolarizing prepulses. A hyperpolarization of only 2 seconds to −90 mV was sufficient to reverse the AQA39 block, while 60 seconds at −90 mV was required for D600. At −140 mV, 2 seconds were sufficient to remove the D600 block. A similar voltage dependence has been reported for diltiazem (178). These results are consistent with a low affinity of these drugs for receptors in rested channels and a shift in the apparent inactivation curve to more negative levels. Similar results have been reported from the study of slow responses (187).

Is Drug-Receptor Affinity Higher in Activated or Inactivated Calcium Channels?

A recent study by Kanaya et al (178) showed that block by diltiazem and verapamil of I_{si} during a test pulse was markedly increased by increasing the duration of a depolarizing conditioning pulse from 100 msec to 2–3 seconds. This suggests that both drugs can block inactivated calcium channels. Moreover, for diltiazem this block could not be enhanced by increasing the voltage of a 30-msec conditioning pulse (one too short to result in much inactivation) from −30 to +80 mV. This was interpreted as evidence that the affinity of diltiazem for the inactivated channel is greater than the affinity for the channel in the open state. Lee & Tsien (177) similarly concluded that diltiazem mostly blocks inactivated calcium channels. Even at concentrations as high as 50 μM, they still could not demonstrate open channel block for this drug. In contrast, nitrendipine and D600 both caused a fast reduction of I_{si} upon opening of the channels. Lee & Tsien interpreted this as evidence for open channel block. It should be noted that under the conditions of their experiments (Ba^{2+} substituted for Ca^{2+}) inactivation is minimized, and consequently inactivation block would be minimized. Nevertheless, as in the case of the sodium channel blockers, it appears that some drugs (e.g. diltiazem) behave primarily as inactivated state blockers, while other drugs (e.g. verapamil, D600) also block open channels. It is not clear whether some drugs exclusively block open channels. Moreover, studies of single channel currents (188) have suggested that calcium channels flicker on and off for a period of time after sensing an activating voltage rather than opening only once, as is the case for sodium channels. If this is the case, then continuing development of block of calcium channels during a long depolarizing clamp might represent block of open

flickering channels as well as inactivated ones. Patch clamp methods will probably be needed to resolve this problem.

Dihydropyridine Calcium Channel Blockers: A Special Case?

Several lines of evidence suggest that there may be important differences between the nifedipine family of drugs and other calcium channel blockers. For example, Schramm et al have reported (189) that a new dihydropyridine (BAY K 8644) has potent *positive* inotropic effects that are competitively inhibited by nifedipine. Second, receptor binding studies (190–194) suggest that nitrendipine and other members of the nifedipine family bind to a common receptor site that differs from but is allosterically linked to, the site or sites at which verapamil and diltiazem bind. Lee & Tsien (177) reported that the IC_{50} for I_{si} suppression was about 100-fold higher than the K_d reported for isotope binding studies. This is not totally unexpected, however, since binding studies determine dissociation constants in fully depolarized membrane fragments, i.e. the highest affinity state. In contrast, Lee & Tsien calculated binding in intact cells at −40 mV. Using computer fitting with our own data, we estimate binding to rested channels to have a dissociation constant in the mM to M range. Thus, as in the case of sodium channel blockers, apparent (measured) potencies can vary between the potencies of the lowest and highest affinity states. However, the possibility that the dihydropyridines produce a qualitatively different sort of blockade must be considered. Kohlhardt & Fleckenstein (195) and Bayer & Ehara (196) found that nifedipine produced a block of I_{si} that had the same apparent time constant of recovery as inactivated channels in the drug-free state. Unfortunately, these authors did not use very short or very long recovery intervals. Kass (197) reported that block of I_{si} in Purkinje fibers by nisoldipine was much less voltage-sensitive than block by D600. His protocol showed that, unlike D600 blockade, the nisoldipine-induced suppression of I_{si} was not removed by rests of up to 120 seconds at relatively negative holding potentials. Also in contrast to D600 results was the observation that use-dependence of the nisoldipine block was minimal or absent. Nitrendipine was similarly found to be almost devoid of use-dependent effect by Lee & Tsien (177) in their study of isolated ventricular cardiac cells when measured at a frequency of 0.05 Hz. In a report of slow responses in K^+-depolarized chick ventricle, Hachisu & Pappano (198) found that verapamil, but not nifedipine or nimodipine, caused a use-dependent block. However, the driving frequency in their experiments was only 0.1 Hz, which is too slow to detect use-dependent block if the recovery time constant of the dihydropyridines is less than 2–3 seconds. This point is clearly made by Lee & Tsien (177), who found a recovery time constant of only a few seconds at room temperature (20–22°C) for nitrendipine, thereby implying that use-dependence can occur with this drug. Molyvdas & Sperelakis (199) reported that mesudipine, another congener of nifedipine, manifested

frequency-dependent block of slow responses for the first 20 minutes of exposure and frequency-independent block thereafter. In an earlier study of nifedipine, Kohlhardt & Haap (200) found that this agent caused a use-dependent depression of slow response action potential overshoot and upstroke velocity in rabbit AV node at a frequency of 0.2 Hz. Therefore, a firm conclusion should not be drawn regarding the state dependence of the block produced by the dihydropyridines until they have been studied over a broader range of driving rates. It is likely that most, if not all, of the calcium channel blockers will be found to have use dependence when they are studied at driving intervals shorter than the recovery time constant.

Site of Action of the Calcium Channel Blockers

The route traveled by a calcium channel blocker to its receptor site has certain parallels with that mapped out for the local anesthetics on the basis of their molecular structure and kinetics (6, 98). It is noteworthy that none of the useful calcium channel blockers are permanently charged and the amines all have pKa's of nine or less. All can be taken up by cells (201) and some structure-contractile activity analyses have been reported (174, 202, 203). These data suggest that the drugs must cross the cell membrane to gain access to their site of action. A study of D890 (the N-methyl quaternized derivative of D600) showed it to be without effect in a standard contractility assay (174). In an important extension of this approach, Hescheler et al (204) showed that extracellularly applied D890 had no effects on calcium-dependent electrical properties of guinea pig myocytes. In contrast, D600 at 50-fold lower concentrations markedly lowered and shortened the plateau of the action potential. However, when administered intracellularly by pressure injection, both drugs caused prompt suppressant effects. Furthermore, after a single pulse injection the block induced by D890 persisted, while that produced by D600 completely disappeared within nine minutes. These results suggest that, when in the charged form, drugs must access the verapamil receptor from the intracellular side of the membrane. No reports comparing intracellular and extracellular application of dihydropyridine drugs were found in our survey. However, Rosenberger & Triggle (205) reported that quaternary analogs of nifedipine were inactive in suppressing smooth muscle contraction, suggesting that these drugs also must cross a lipid barrier to gain access to their receptor.

As noted above, dissociation of uncharged local anesthetic drugs from the inactivated sodium channel probably takes place through the lipid phase of the membrane. Such studies require the availability of similar drugs with different lipid:water partition coefficients, or a single drug whose partition coefficient can be modified by pH manipulation. Whether size is a more important determinant of the recovery time constant than lipid solubility for calcium channel blockers, as it is for local anesthetics (35), will require further inves-

tigation. However, Pelzer et al (186) found that for the closely related drugs, D600 and AQA-39, the less lipophilic and slightly smaller molecule AQA-39 had the faster rate of dissociation.

APPLICATIONS OF THE MODULATED RECEPTOR HYPOTHESIS

Selective Depression of Depolarized Tissue

Arrhythmias are frequently associated with tissue depolarization caused by a variety of conditions, but especially ischemia (64, 206–213) and digitalis poisoning (214, 215). For several reasons, antiarrhythmic drugs are more depressant in depolarized tissue (Table 5). First, receptor binding of these drugs develops faster and dissociation occurs more slowly in depolarized myocardium. As a result, the clinician (under optimal circumstances) can choose a drug dose that will have relatively little effect on normally polarized tissue, which is necessary for normal conduction, while selectively depressing the depolarized tissue, which is responsible for the arrhythmia.

Second, although all antiarrhythmic drugs appear to shift inactivation and slow recovery, one would expect, other factors being equal, that an inactivation blocker would be more selective than an activation blocker when the major basis for the arrhythmia is depolarization.

Selective depression of depolarized tissue is now well accepted as a major mechanism of action of sodium channel-blocking antiarrhythmic drugs (2, 3, 63, 242, 255, 256).

Table 5 Evidence for selective depression as an effect of sodium channel blockers

Drug	References
Aprindine	41–43
Disopyramide	124,216,217
Encainide	218–220
Ethmozin	221
Flecainide	222–224
Imipramine	225
Lidocaine	30,34,61,62,69,93,96,226–246
Mexiletine	71,73,75,76,247,248
Phenytoin	62,227,249–251
Prenylamine	79
Procainamide	62,80
Propafenone	81,83
Propranolol	62,252
Quinidine	62,240
Tocainide	61,253,254

In the case of the calcium channel blockers, the situation is somewhat complicated by the very significant protective effect of these agents in metabolically compromised tissue (257–262). In several acute coronary occlusion and reperfusion models, diltiazem and verapamil are extremely effective in preventing arrhythmias (263–265). They are less effective in suppressing arrhythmias after they have started (266, 267). There are several possible explanations for this discrepancy; protection against depolarization caused by ischemia when given before occlusion or reperfusion is one (268).

Selective Depression of Tachycardias

During a rapid rhythm, i.e. one with short diastolic intervals, less recovery from drug-induced blockade can occur between beats than during a slower rhythm. Also, more activation and inactivation block develops. Hence, the shorter the cycle length, the greater the steady-state block of inward currents. Thus, given a drug with a long recovery time, e.g. quinidine, one can choose a dose that minimally reduces conduction at normal heart rates but suppresses conduction in a tachycardia. For some other drugs, e.g. lidocaine, the diastolic recovery from block at normal resting potential is so fast that they are not very effective in "filtering" tachycardias. Thus, it has been reported by numerous investigators that lidocaine is not a very effective agent in ventricular tachycardia in the absence of resting depolarization (269–271). However, lidocaine is still effective in preventing very fast arrhythmias, e.g. ventricular fibrillation (272). Nifedipine, which manifests little or no use dependence of blockade at slow and moderate driving rates, also turns out to be ineffective in reversing supraventricular tachycardias (273), the arrhythmia in which other calcium channel blockers are most effective.

Selective Depression of Early Extrasystoles

An early extrasystole can be viewed as a very rapid single beat tachyarrhythmia. Because the tachycardia is not sustained, a drug that produces a slowly increasing use-dependent block will not block such extrasystoles very effectively. The primary example of a drug that has such a pattern of slow in-slow out (SISO) blockade is quinidine. That is, development of block is slow and recovery during rest is also slow. In contrast, a drug like lidocaine can be described as fast in-fast out (FIFO), since it associates avidly with the receptor during the entire duration of the action potential and dissociates rapidly during diastole. Hence, a sufficiently early extrasystole will find a significant fraction of channels blocked—and will be suppressed—at doses of lidocaine that have little depressant effect on impulses in the normal rhythm. Therefore, for a given tolerable (minor) depression of the normal rhythm, a FIFO drug will provide much more depression during diastole than a SISO agent.

Instances often occur in which FIFOs are not quite effective, and the

maximum tolerated level of a SISO also does not achieve the required suppression of the extrasystoles. It can be computed (34) that the combination of a FIFO agent (lidocaine or equivalent) with a SISO drug (quinidine) can provide a therapeutic efficacy not obtainable with maximum tolerated doses of either drug alone. This prediction has been confirmed by experimental (274) and by clinical studies (275, 276).

The other permutations of the rate in-rate out description are easily predicted. A slow in-fast out agent would be ineffective and would probably be dropped from study in early screening tests. In contrast, a fast in-slow out agent (rapid association, slow dissociation) might be expected to have a high degree of cumulation, i.e. would be a potent local anesthetic. If, however, such an agent was accidently administered systemically, it would be toxic to the myocardium at slow heart rates and relatively low plasma concentrations. Bupivicaine appears to be such a FISO drug (277).

Selective Depression on the Basis of Action Potential Duration

The experiments utilizing modulated receptor protocols described above show that certain drugs are nearly pure inactivation blockers, (e.g. amiodarone, benzocaine, diltiazem), others are nearly pure activation blockers (e.g. quaternary lidocaine derivatives, quinidine), while most of the drugs have significant affinity for the channel receptor in both states. Since the action potentials of all cardiac tissues have an upstroke of roughly comparable duration (1–2 msec), activation blockers are expected to be effective in all tissues. In contrast, the plateau of the action potential varies markedly in different cardiac cells (50–500 msec). The effect of an inactivation blocker will be more marked the longer the duration of the action potential plateau (13). Thus, inactivation blockers are expected to be more effective in Purkinje and ventricular myocardium than in atrial tissue. Moreover, if the inactivation blocker also has a fast diastolic recovery, the drug will produce an insignificant level of block in atrial tissue and will have little efficacy. Lidocaine in atrial tissue would therefore behave like a slow in-fast out drug; and it does have a low efficacy against atrial arrhythmias (234).

Antiarrhythmic Drug Interactions Caused by Receptor Modulation

Since many cardiac drugs can lengthen or shorten the cardiac action potential duration, it is predictable that these drugs might potentiate or antagonize the action of inactivation blockers. Thus, part of the positive interactions observed between quinidine and mexiletine (276) must result from the lengthening of the action potential duration caused by quinidine, which provides more time for inactivation block by mexiletine to occur. It will be important to see whether drugs that cause more marked lengthening will further amplify this synergistic

action. Conversely, shortening of action potential duration would theoretically be of benefit in the treatment of toxicity caused by inactivation blockers.

In summary, modulated receptor concepts appear to be well supported by the available experimental evidence. However, the hypothesis cannot yet be considered to have been *proven* to be the sole or primary mechanism of the action of these drugs (278). Further tests over broader experimental conditions need to be carried out. One of the major advantages of the hypothesis is the wide range of testable predictions that can be generated. As noted above, many in vitro studies in the last five years have been designed on this basis. It is hoped that in the next five years, many more clinical as well as basic studies will test the hypothesis.

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