Antiarrhythmic agents: modulated receptor applications

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IT IS NOW well established that block of transmembrane ionic channels is frequently time and voltage dependent.\(^1,2\) Although the modulated receptor theory has been most extensively studied for sodium and calcium channels in cardiac tissue,\(^3\) it may apply to other membrane receptors as well. The present essay is limited to discussion of sodium-channel blockers and how their time- and voltage-dependent block can contribute to antiarrhythmic and arrhythmogenic actions. After a brief description of the modulated receptor theory and the definition of some commonly used but ill-defined terms, these principles will be applied to some clinical conditions. Although the general flavor of the present article should be palatable without studying previous reports describing the modulated receptor hypothesis, full appreciation of all the concepts may require some additional reading.\(^2,4\) It is my hope that these considerations will spark some tests in vivo of the modulated receptor concepts that will ultimately benefit the patient suffering from arrhythmias.

Basic concepts

The modulated receptor hypothesis. According to Hodgkin and Huxley, sodium channels exist in three primary states (figure 1): rested (\(R\), a closed state most prevalent at negative membrane potentials), inactivated (\(I\), a closed state at depolarized membrane potentials), and open or activated (\(A\), the state through which the channels pass upon depolarization when they move from the \(R\) to the \(I\) state). Applied to cardiac tissue this means that the \(R\) state is most prevalent during diastole, the \(A\) state during the upstroke, and the \(I\) state during the plateau or when the tissue is depolarized (e.g., by ischemia). The modulated receptor theory states that drug affinity for a specific receptor on the channel is modulated by channel state, i.e., each sodium-channel blocker has a characteristic association (\(k_R\), \(k_A\), and \(k_I\)) and dissociation (\(l_R\), \(l_A\), and \(l_I\)) rate constant for channels in each of these states. Although drug-associated channels (like drug-free channels) distribute between rested (\(R'\)), activated (\(A'\)), and inactivated (\(I'\)) states in a voltage-dependent fashion, they may not conduct sodium and may have altered voltage dependence for their state transitions: they behave as if the membrane potential was less negative. As a result, blocked channels tend to accumulate in the \(I'\) state.\(^4\)

Although at high enough concentrations blockers may bind to the channel receptor in any state, clinically useful agents will block activated channels (e.g., quinidine), inactivated channels (e.g., amiodarone), or both (e.g., lidocaine), but they will usually have a relatively low affinity for rested channels. Indeed, a drug that preferentially blocks rested channels would reduce conduction in normally polarized tissue where channels are predominantly in the \(R\) state, while interfering less with conduction in depolarized tissues where more of the channels are in the \(I\) state. Such a drug would be predicted to be arrhythmogenic.

Tonic block refers to the drug-induced reduction of channel availability after a long rest period. Contrary to common presumption, tonic block does not only represent block of rested channels, but also can result from block of open or inactivated channels. Indeed, block of open channels that develops at any time before the maximum upstroke velocity of the cardiac action potential or the peak of the sodium current (when the measurement of sodium channel availability is made) will appear as tonic block. Similarly, at membrane potentials where only a small fraction of the channels is inactivated, block of inactivated channels will trap channels in the \(I'\) state and will appear as tonic block.

Use-dependent block refers to drug-induced reduction of channel availability exceeding the tonic block and is caused by use of the channels. It results whenever the affinity for open or inactivated channels exceeds the affinity for rested channels. Consequently,
Open- vs inactivated-channel block. With a few exceptions, it is irrelevant whether block develops while the channels are open (upstroke) or inactivated (plateau); only the amount of block developing with each action potential is important. The exceptions include the following: (1) The reduction of the sodium current by drugs that block open channels is not a function of action potential duration, but drugs that block inactivated channels may have more effect in tissues that have long action potential durations (e.g., Purkinje fibers) than in tissues that have shorter action potential durations (e.g., atria). (2) Blockers of inactivated channels may depress abnormal conduction in depolarized tissue better than blockers of open channels, because depolarization promotes the inactivated state. (3) In depolarized tissue, block of open channels may become compromised: block of open channels is strongly voltage dependent (figure 2). Since the overshoot of the action potential becomes progressively more negative as tissue depolarizes, a blocker of open channels may progressively lose its effectiveness. (4) The upstroke of the action potential always precedes the plateau. Thus, when combining two drugs, a blocker of open channels may, by binding first, prevent a blocker of inactivated channels from binding (e.g., see lidocaine and bupivacaine example below).

Recovery from block. The amount of block developed...
per action potential and the rate of recovery from block during diastole together determine the net block produced by a drug. According to the modulated receptor scheme the drug has three pathways to dissociate from the channels (R' to R, A' to A, and I' to I). At normal to depolarized potentials drug-associated channels accumulate in the I' pool, because the potential at which drug-associated channels go from the I to the R state is more negative than that for drug-free channels. Thus, at these potentials unblocking from I' to I is available, especially to lipid-soluble drugs. If the membrane potential is negative enough to overcome the altered voltage dependence of blocked channels, then a significant fraction of the drug-associated channels may go from the I' to the R' state during diastole. As a result, two additional routes for recovery from block become available: the R' to R, and during the subsequent opening, the A' to A pathway. The availability of these additional faster pathways at more negative potentials is responsible for the rapid recovery from block at these potentials. For lipid-insoluble compounds (e.g., quaternary compounds) or the cationic form of weak acids and bases, the A' to A may actually be the primary pathway for recovery from block.

pH. Most antiarrhythmic agents are weak bases that exist in the cationic and neutral form at physiologic pH. Acidosis, as occurs in ischemic tissue, promotes the cationic drug form, which dissociates more slowly from the receptor; hence, greater block results at any given heart rate and so antiarrhythmic drugs can selectively depress conduction in acidic tissue. Conversely, alkalization promotes the neutral form of the drug and hence speeds up recovery and reduces sodium-channel block. This pH dependence may explain the clinical utility of alkalization in toxicities resulting from excess block of sodium channels.

Clinical implications

In a recent review, Hondeghem and Katzung described in detail how application of the modulated receptor theory can account for selective depression of electrical activity in depolarized tissue, tachycardias, and early extrasystoles. Rather than reiterating these three important concepts, I will now take the opportunity to introduce six new concepts that derive directly from the modulated receptor concept.

Therapeutic safety and efficacy. The balance between block development during the action potential and recovery from block during diastole determines the level of sodium-channel block. For drugs that block open or inactivated sodium channels, block develops during the action potential, and gradually decreases during diastole with a time constant that is a function of membrane potential and pH, but specific for the individual drug. The main portion of figure 3 represents the maximum percent block that may be present at the beginning of diastole so that no more than 20% of the block (arbitrary maximum allowable) persists at the end of a 600 msec diastolic interval as a function of the time constant of recovery (curve labeled “O”). When recovery is very fast (e.g., lidocaine) channels may be 100% blocked at the start of diastole and yet recover to less than 20% block after 600 msec; when recovery is very slow (e.g., flecainide), block of more than 20% of channels will cause excessive block at the end of diastole.

For this maximum amount of block the percent block at various diastolic times (20, 40, 75, 150, 300, and 600 msec) was also computed. It is clear from the figure that a drug with a time constant of recovery of 373 msec (at arrow on abscissa) maintains the most block for the longest time. Indeed, only for this time constant can 100% of the channels be blocked at the beginning of diastole, while only 20% remain blocked at the end of diastole (see inset tau = 373 msec). For drugs with shorter time constants (figure 3, inset tau = 100 msec), block does not persist long enough, while for drugs with longer time constants (figure 3, inset tau = 10,000 msec), the achievable maximum is reduced. Although the curves computed in figure 3 would be different for different assumptions about maximum allowable block and diastolic time, there still would exist an optimal time constant of recovery for a drug that would provide maximum diastolic block for any allowable end-diastolic block.

It should be noted that the time constant of recovery is frequently strongly voltage and pH dependent, and under abnormal conditions in which arrhythmias are likely to occur (e.g., depolarized membrane potential or more acid pH) the time constant of recovery could be much longer. Hence, from figure 3 it is clear that a level of early diastolic block by a drug with a given time constant of recovery that is well tolerated in the normal tissue could be much more depressant in the arrhythmia-prone condition in which the same drug could have a much longer time constant; i.e., antiarrhythmic drugs depress electrical activity selectively in the parts of the heart subjected to these abnormal conditions.

The difference between the blocking capability under the arrhythmogenic condition and that in the normal condition then determines the therapeutic safety. Agents that have long time constants, e.g., so-called class Ic agents, do not discriminate well between nor-
mal and depressed tissue (figure 3; once a time constant is long, making it still longer does not make much difference), and consequently they are expected to have a lower therapeutic index. Thus, it is not surprising that the incidence of arrhythmia induction with drug therapy increases as the drug’s time constant of recovery lengthens.9 I hope that the present trend to search for more potent antiarrhythmic agents that are tested in patients who do not respond to classical class Ia and Ib agents does not lead to a "rush to class Ic drugs." Indeed, it is efficacy and safety and not potency that matters, and selecting agents for potency in nonresponders may result in the next crop of antiarrhythmic agents being less safe.

Synergistic combinations. In 1980, Hondeghem and Katzung10 predicted, based on modulated receptor simulations for two drugs, that drug combinations could provide diastolic block that could not be attained by either drug alone. It has now been demonstrated by numerous groups that in selected patients, combination of drugs with different kinetics can provide more protection with fewer side effects (for example see Duff et al.11).

Figure 3 shows that for a particular set of circumstances there exists an optimal time constant of recovery to achieve maximal block throughout diastole. Although it is virtually impossible to estimate this time constant for any particular clinical condition, the combination of a slower and a faster drug (figure 3, inset tau = 100 and 10,000 msec) will provide more block

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**FIGURE 3.** Maximum achievable block at beginning of diastole (curve labeled “O”) that at end of a 600 msec diastolic period results in no more than 20% block (arbitrarily chosen maximum that induces no toxicity of regular heartbeat) as a function of the time constant of recovery from block. For this maximum the block at diastolic times of 20, 40, 75, 150, 300, and 600 msec was also computed. On the abscissa time constants for lidocaine, procainamide, quinidine, and flecainide in normal tissue are indicated. Under these conditions the most diastolic block is maintained for the longest possible time for the time constant of 373 msec (arrow on abscissa). The block as a function of diastolic time for this 373 msec time constant of recovery is plotted in the center top inset. For reference purposes it is also represented in all other insets as a dotted line. The top left inset illustrates the time course of maximum allowable diastolic block for a drug with a shorter time constant of recovery (tau = 100 msec), while the top right inset shows this for a longer time constant (tau = 10,000 msec). The bottom inset shows the maximum achievable block by the combination of two drugs (solid line) with time constants of 100 and 10,000 msec. For reference the maximum achievable block by a drug having a time constant of recovery of 100 (dashed line), 373 (dotted line), or 10,000 msec (dot-dashed line) is also shown. Clearly the combination can achieve more diastolic block than each of the individual drugs of the combination, i.e., it better approaches the maximum achievable block by the drug with a time constant of recovery of 373 msec.
than the slower or the faster drug alone. Obviously, as the time constants for the slower and faster drug more closely approach the optimal time constant, the maximum achievable block will be approached. Similarly, the combination of two drugs with very similar time constants (for example, two class lc agents) is not expected to be of great benefit. The present computations may provide a rational basis for optimizing synergistic combinations.

Some antiarrhythmic agents such as amiodarone appear to be quite effective even though they are not very potent sodium-channel blockers. This agent appears to be endowed with class I, II, III, and IV properties. However, it should be remembered that arrhythmias are electrical disturbances of the heartbeat resulting from multifactorial perturbations (metabolic, humoral, anatomic, ionic [Na\(^+\), K\(^+\), and Ca\(^{2+}\)], nonuniform distribution of electrophysiologic properties, etc.), and therefore it may not be surprising that agents with multiple actions may be quite effective. One should question, however, whether amiodarone, with its fixed combination of activities (not all of them very effective) and high incidence of serious toxicity could not be outperformed by a careful titration of the individual components of more effective and less toxic drugs.

**Antagonistic combinations.** An important implication of the modulated receptor theory is that reduction of the sodium current by antiarrhythmic agents is not the result of a nonspecific membrane disturbance, but rather of a drug interaction with a specific receptor site on the sodium channel. There exists an important and experimentally testable difference: in the nonspecific membrane disturbance model, addition of a second drug should always further reduce the sodium current; on the other hand, in the specific receptor model, addition of a drug with a shorter time constant of recovery to another drug with a longer time constant can result in an *increase* of the sodium current (under suitable conditions) by competitive displacement. Indeed, if the slower drug is present in high enough concentration to block a significant fraction of the sodium channels per action potential and has a short enough time constant to result in a significant unblocking during diastole, then the faster drug may competitively displace the slower one from sodium-channel receptors. These channels will then recover more quickly, and the block present at the end of diastole may be reduced. Such competitive displacement of bupivacaine by lidocaine has been demonstrated experimentally.\(^{12}\)

Lidocaine, which has a time constant of recovery of about 180 msec at the normal resting potential, should be able to competitively displace all compounds that have longer time constants (“slower” drugs). However, if the time constant of the slower drug becomes too long (e.g., flecaïnide), the fraction of channels that can be competitively displaced (i.e., block and unblock per cycle) is very small and hence little antagonism is possible. Actually, in clinical concentrations quinidine blocks and unblocks too little for significant displacement to occur. Hence, as described above addition of lidocaine to quinidine in clinically relevant doses will mostly result in extradiastolic block, with little or no reduction of block for the regular heartbeat.

Since bupivacaine can readily be displaced by lidocaine,\(^{12}\) I predict that agents with similar time constants of recovery (e.g., amiodarone [1.6 sec]; procainamide [2.3 sec]) or shorter time constants (e.g., mexiletine [360 msec]; tocainide [550 msec]) could also be readily displaced by lidocaine, at least under conditions in which they produce substantial use-dependent block.

It should be noted that blockers of open channels will inherently be better able to reverse sodium-channel block than blockers of inactivated channels with identical time constants of recovery. Indeed, open-channel blockers can sequester channels first (opening precedes inactivation) and deprive the blocker of inactivated channels from an equal opportunity to block channels. For the same reason, a faster blocker of inactivated channels will have an advantage over a slower blocker.

A special case of drug interactions, but perhaps a very important one, relates to metabolites interacting with the parent compound. A metabolite with slower kinetics of recovery from block than the parent compound may elicit synergistic interactions. Conversely, a faster metabolite might competitively antagonize the parent compound. It has been demonstrated recently that glycerylxyline exhibits both synergistic and antagonistic interactions with lidocaine for the sodium-channel receptor.\(^{13}\) Although until a study in patients is finished it cannot be proven that these interactions are clinically very important for glycerylxyline and lidocaine, it is nevertheless probable that competitive displacement of a parent compound by a metabolite is an important principle to consider for any drug.

**No effect** drugs. No-effect drugs may increase selectivity of antiarrhythmic drugs. Drugs with very fast time constants of recovery (tau \(\leq 10\) msec; figure 3, *left*) could have little effect on their own; they block the sodium channel for too little time. Actually, the effects of these chemicals are so small that they probably would be missed as sodium-channel blockers by common tests. However, agents with these properties
might provide ideal competitive displacers to treat an overdose. More importantly, if such an agent had a voltage-dependent selectivity so that it avidly displaced competing drugs in normally polarized tissue, but little in depolarized tissue, then it could augment the efficacy and therapeutic safety of currently used antiarrhythmic agents. Actually, since antiarrhythmic drugs block and unblock more in well-polarized tissue than in depolarized tissue, such a no-effect drug would antagonize effects of antiarrhythmic drugs selectively in the normal tissue.

**Fibrillation occurring soon after ischemia.** Even though we do not know all the details of what ultimately precipitates ventricular fibrillation, shortly after an acute ischemic episode it is known that changes in cardiac tissue evolve from relatively normal conduction to inexcitability. These two extremes are separated by a window in time where the tissue becomes critically depressed (abnormal conduction: unidirectional block and slow conduction) so that serious arrhythmias, including fibrillation, become likely. In rabbit hearts under control conditions the first serious arrhythmias developed after about 6 min of ischemia and the tissue became inexcitable about 2 min thereafter. In the presence of antiarrhythmic drugs, after ischemia arrhythmias and inexcitability developed progressively earlier as the drug dose was increased. Since in the presence and absence of drug the onset of arrhythmias coincided with an increase in threshold stimulation current of about 100%, and inexcitability ensued shortly after the threshold had increased to about 250%, these values are used as the delimiters for "critical" depression in figure 4. (Although in other hearts the timing of arrhythmias may be somewhat different, or one might want to select other minimum and maximum values for critical depression, the conclusions below remain unchanged.) Accordingly, as the concentration of lidocaine administered before the onset of ischemia is increased, the window of critical depression occurs earlier and is narrowed.

Numerous reports in the literature indicate that the effectiveness of lidocaine to prevent the occurrence of ventricular fibrillation varies from very effective, to little or no effect, to precipitation of fibrillation (for a recent review see Carson et al. 15). All these reports are compatible with the results in figure 4. In experiments in which the ischemic period is terminated before the occurrence of the control window but after the lidocaine window, serious arrhythmias and fibrillation are expected to occur earlier and more frequently in the presence of drug than at control. 15 High concentrations of lidocaine shorten the duration of the critical window and hence may reduce the incidence of fibrillation.

More importantly, careful examination of the experimental results in figure 4 indicates that administration of a low therapeutic (7 μM) or high therapeutic

![Figure 4](http://circ.ahajournals.org/)

**FIGURE 4.** Windows of critical depression of electrical activity in ischemic tissue in the presence and absence of lidocaine.
(20 μM) concentration of lidocaine at 5 min after ischemia would immediately render the tissue inexcitable before it could become arrhythmogenic. Between 4 and 5 min, 20 μM also would effectively suppress electrical activity before arrhythmias developed, but 7 μM would render the tissue critically depressed, promoting arrhythmias. However, premature administration of antiarrhythmic drugs may well be arrhythmogenic, precipitating critically depressed conduction or by making the window of critical depression occur sooner. Thus, the optimum strategy may be to apply the right dose (minimum necessary, but less than that which critically depresses the normal tissue) at the right time (when it will promptly suppress the critically ischemic tissue).

In conclusion, since arrhythmias frequently have a multifactorial origin, widely varying characteristics, and evolving nature, it is unlikely that a single drug (even one with multiple actions) will optimally reduce their incidence under a broad range of circumstances. Rather, optimized therapy may involve carefully titrated drug combinations. Nonoptimized drug administration may do more harm than benefit. Finally, study of drugs in patients whose conditions are resistant to all traditional agents may bias the discovery of new antiarrhythmic agents in favor of agents that are less effective against more common arrhythmias, or overlook the more universally effective agents all together.

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