

Special Article

On Looking at Electrical Activity of Heart Muscle

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ACTIONS of drugs on the heart can be conveniently divided into those on the electrical properties of the membrane, those on contractility, and those on the intermediate stage of so-called excitation-contraction coupling. Blinks has recently commented on myocardial contractility in this Journal,¹ and with Jewell elsewhere.² Our knowledge of excitation-contraction coupling has not yet reached a stage such that a nontechnical review would be very meaningful. We do know a good deal about electrical events and, in fact, many discussions of the electrical properties of heart muscle and the effects of drugs on these properties are available.³ However, the reader is often left with the feeling that the whole field is extremely complex, not very well understood, or both. This need not be the case. Although cardiac electrophysiology is somewhat complex and although many details have not yet been worked out, the area has reached the stage where a general pattern is emerging and a systematic approach to the analysis of actions of drugs can be developed. We should like to present one such approach and to illustrate it with an analysis of the actions of acetylcholine. This agent has been studied thoroughly enough that a sufficient number of pieces are available in the jigsaw puzzle to indicate what the final picture will be. To a certain extent our analysis may be premature because all the facts are not available in as rigorous a form as would be ideal. Probably some of the details in the fol-

lowing presentation will need revision with time. Nevertheless, the general approach can be expected to give a reasonable description of what is going on, and familiarity with this sort of analysis is useful.

We shall 1) begin by reviewing the classical approach to the description of the action of drugs on the heart, and indicate some limitations in this approach; 2) then describe the more fundamental approach now appropriate in the light of the extensive studies of the last ten years; 3) then examine the actions of acetylcholine in this frame of reference, in particular to indicate that all the actions of this agent can be interpreted as the result of a single effect on the cell membrane; 4) finally, discuss other drugs, particularly those of therapeutic interest. Unfortunately, with none of the latter are we able to provide as satisfying a picture as is possible for acetylcholine. This is simply because drugs other than acetylcholine have not yet been studied to the same extent. We shall only be able roughly to indicate the form of pharmacologic description which ultimately we would like to be able to use.

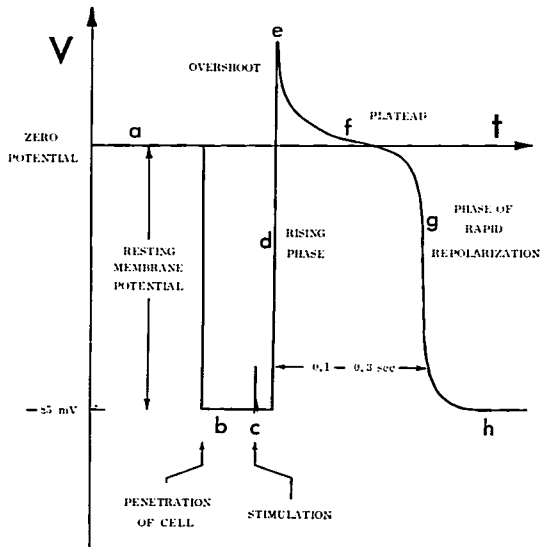
THE CLASSICAL APPROACH

Traditionally the actions of drugs on the heart have been classified in terms of actions on contractility (inotropic effects), automaticity or spontaneity (chronotropic effects), conduction velocity (dromotropic effects), and excitability (bathmotropic effects). The first term refers to the effect on the contractile elements; the last three, to the effects we will be discussing here—effects on electrical activity. As will become apparent, the distinction between effects on conduction and on excitability, for example, is artificial because these effects are not independent. Furthermore, because automaticity, excitability and conduction are not fundamental properties their use for classifica-

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³ See Hoffman and Crane's monograph³ or Trautwein's review.⁴ These articles give the references to the original observations. To make the present discussion as compact as possible, we have not documented experimental observations unless they were particularly relevant.

FIG. 1. Scheme illustrating the basic features of a cardiac action potential (in this case, from a ventricular fiber). Abscissae: time. Ordinates: voltage recorded by a fine intracellular electrode. Bath potential defined as zero. With the insertion into a cardiac cell, a negativity of about 80-90 mV is seen (b). Stimulation (signalled by the small upward deflection c of the shock artifact) leads to the complex of changes called an action potential. These include the upstroke (d), overshoot (e), plateau (f) and repolarization (g) to the resting level (h).



tion of drug actions cannot be expected to increase understanding of the system. A description of drug action based on these terms tends, therefore, to lead to an empirical listing of a large number of apparently unrelated and possibly bizarre facts. For example, acetylcholine has been said to increase, decrease or not alter the conduction velocity in the atrium.⁴⁻⁶ Such conflicting observations appear confusing, but they seem less so if viewed as results of changes in the permeability of the excitable cell membrane.

The Electrical Properties of Cell Membranes of Cardiac Muscle

INTRODUCTORY REVIEW

It has been known for a long time that signals are transferred from one part of the heart to another by an electrical mechanism. In fact, it is the field generated by these signals that is measured when one records an electrocardiogram. Since the turn of the century these signals have been considered to be derived from a potential difference across the cell

membrane. It became possible to record the membrane potential directly with development in the mid-fifties of every fine microelectrodes which could be inserted into the small (15 microns) cardiac cells without killing them. (The electrodes are made by pulling capillary glass tubing out so that it tapers to a tip of submicroscopic dimensions—of the order of 0.5 microns or less. The lumen survives this maneuver! Such pipettes are filled with a conducting solution, typically a concentrated solution of potassium chloride, so that when inserted into a cell they provide a direct electrical connection with its interior.)

To focus our ideas, let us imagine that we have such an electrode poised over a piece of cardiac muscle immersed in a physiologic salt solution (*i.e.*, immersed in a fluid mimicking the normal extracellular environment). Let us record voltages relative to that in the bathing solution. Since the electrode is in the solution, we begin by recording zero volts (*a* in fig. 1). Now let us lower the electrode gently; when it reaches one of the superficial muscle cells, its own weight will drive it through the cell

membrane into the interior. At this point we record a sudden drop in voltage of about a tenth of a volt (80-90 mV), *i.e.*, as in nerve and other excitable cells, the inside is negative relative to the outside (*b* in fig. 1). This voltage difference is the "resting membrane potential." Except in some specialized cells (see below), this resting potential does not change with time unless the tissue is stimulated. Suppose we stimulate the cell by applying a brief electrical shock. (The shock usually disturbs the recording system briefly to produce the small shock artifact, "*c*" in fig. 1). The stimulus initiates the characteristic response (*d-g* of fig. 1)—the "action potential." The membrane potential rises very rapidly (*d*) and the cell becomes positive inside ("overshoots" zero potential *e*); then the membrane potential falls back part way, stays at this "plateau" potential (*f*) and then later rapidly returns (*g*) to resting levels (*h*).†

Two points may be made at this time. First, the shape of the action potential varies among different parts of the heart (fig. 2), and second, the duration of the action potential is considerably greater in cardiac muscle than in skeletal muscle or nerve—tenths of seconds vs. milliseconds.

Cardiac cells may be classified into two types—those with a stable resting membrane potential, as just described, and those in which a stable resting potential cannot be found. Typically, the latter type is found in the sinoatrial node and, in less marked form, in the atrioventricular node and conduction system. During diastole these unstable cells have a tendency to depolarize spontaneously, that is, a tendency for the inside to become less negative. As a result, they will reach their own threshold for excitation spontaneously, and, therefore, initiate an action potential. As soon as this action potential is over, the whole process begins again. The resulting series of action potentials spreads to adjacent cells, exciting them, so the spontaneous cells behave as "pacemakers." The spontaneous diastolic de-

polarization is known as a "pacemaker potential" (examples from the sinoatrial nodal region are shown in fig. 2A, B, C).

Many cells in the heart have pacemaker activity but in varying degrees. The cell that reaches threshold soonest triggers the others and, therefore, dominates. The others, called "latent pacemakers" (fig. 2D, E, I, J), show a spontaneous depolarization in diastole with a sharp break at the point at which they are triggered by the dominant pacemaker.

All the voltage changes described above can be interpreted in terms of ionic concentration gradients and permeabilities. We shall now discuss the relationship of these factors in detail.

THE RESTING MEMBRANE POTENTIAL

Direct measurement shows that there is a high concentration of potassium and a low concentration of sodium inside cells, and the reverse outside. The cell membrane separating the two solutions is permeable to both ions, but far more to potassium than to sodium; it is this differential permeability that makes the inside negative. To see how this comes about, suppose the membrane were permeable only to potassium. Potassium ions would start to leave the cell because their concentration is lower outside. Sodium ions would try to enter where the concentration is lower but would not be able to do so because the membrane blocks their passage. The net result would be a deficit of positive potassium ions on the inside, *i.e.*, the inside would become negative. This negativity would increase until its pull was enough to balance the concentration gradient driving the potassium out of the cell. At this point, equilibrium would be reached and the inside would be about a tenth of a volt negative to the outside, given the concentration gradients normally present. Next, suppose the membrane were permeable to sodium only. In this case the inside would become positive. Finally, we come to the situation in an actual resting membrane—potassium permeability is much greater than sodium permeability. The membrane can be expected to come to a level at which the inside is negative but not quite so negative as it would be were there zero membrane permeability to sodium.

† In the literature these phases of the cardiac action potential have been labelled with the numbers 0 (upstroke) through 4 (diastole). These labels add no information and, in fact, make it difficult for the person not in the field to follow discussions. Use of descriptive terms like phase of repolarization is preferable.

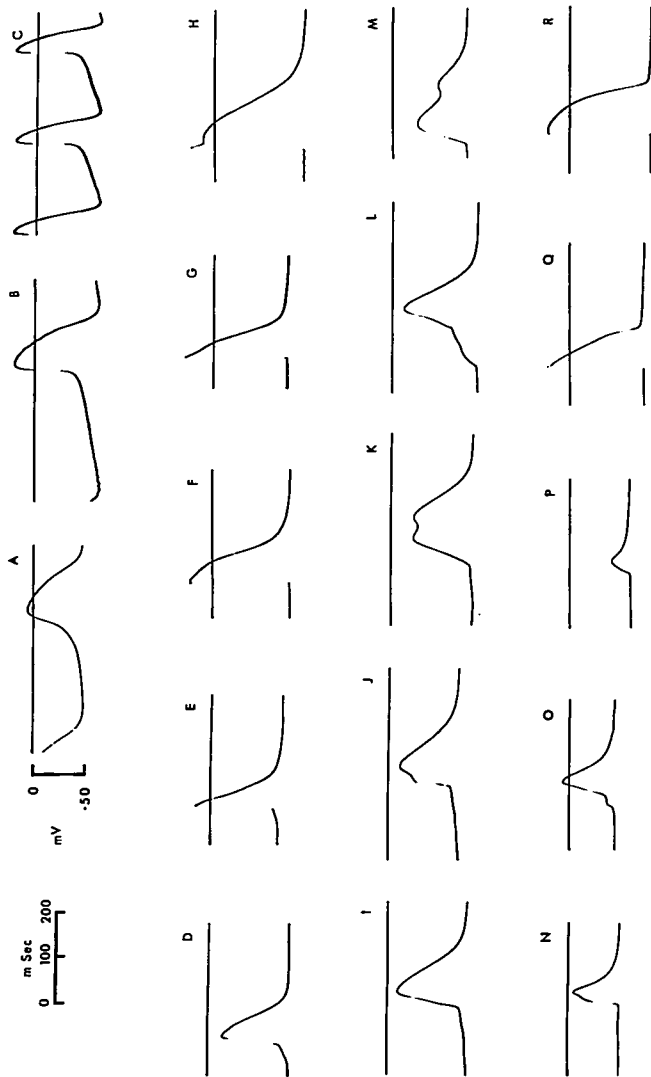


FIG. 2. Examples of action potentials from different parts of the heart. Electrical recordings made as discussed in connection with figure 1. Horizontal line gives zero potential. Voltage scale (ordinates) and time scale (abscissae) shown at top left for all panels, except C where the time scale is slowed twofold. A: rabbit sinoatrial node. B and C: near sinoatrial node of rabbit. D and E: rabbit atrium, still further from the sinoatrial node. Latent pacemaker activity visible. F: guinea pig atrium. G and H: rabbit atrium. I-M: guinea pig atrioventricular nodal region. N-P: rabbit atrioventricular nodal region. I through P show variability in this area and humps which suggest that spatial summation is occurring. Tracing P is from a preparation in which nodal block happened to occur. Q and R: papillary muscle of rabbit and kitten, respectively, indicating ventricular action potentials. (When the membrane potential shifts rapidly during the upstroke of the action potential, the trace can be too faint to expose the film properly. The tracings have not been retouched, so the upstroke is faint or absent in some panels.)

In other words, we picture a *scale of possible membrane potentials running from the internal negativity (E_K) to be expected if the membrane were permeable to potassium only to the internal positivity (E_{Na}) expected if the membrane were permeable to sodium only*. Note that the voltage difference across the membrane can be varied over this whole range by changing membrane properties (relative permeability to the two ions). Once the concentration gradients are given, E_{Na} and E_K are defined and we can forget about ionic concentrations and mechanisms such as the sodium pump that maintain them. Movements of ions across the membrane during an action potential are not great enough to affect the concentrations appreciably. Further description of the electrical properties of cardiac cells will, therefore, involve consideration of permeabilities of the membrane to sodium and potassium (P_K and P_{Na}). We have thus identified the fundamental parameters for the description of the electrical events in which we are interested.

(Since electrical events can be pictured most simply in terms of permeabilities, we consider these more fundamental than parameters like conduction velocity. However, this is not to imply that permeability stands alone in this regard nor that it is as fundamental as one can get. Other factors like membrane capacitance seem equally "fundamental." However, it is possible to work with no more than permeabilities and still get an accurate description. For simplicity, we have chosen to do so. Ultimately, one can reasonably expect that a fundamental description will be phrased not in terms of ionic permeabilities but in terms of physicochemical parameters chosen in light of knowledge of the chemical structure of the membrane. However, the details of this structure are still unknown, so at present we do the best we can and work in terms of permeabilities.)

THE ACTION POTENTIAL

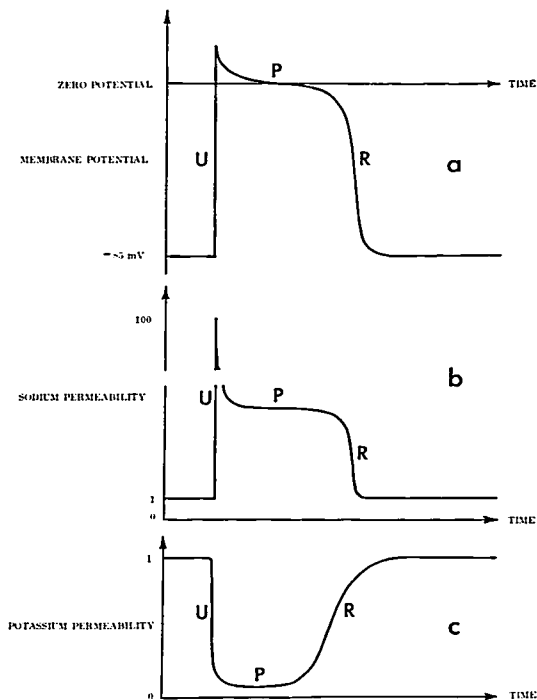
The mechanism underlying cardiac action potentials resembles that in nerve and skeletal muscle to a certain extent, since in all three tissues the action potential is the result of an interplay of changes in permeability to sodium

and potassium. In nerve and muscle the action potential results from a transient increase in permeability to sodium followed by a delayed increase in permeability to potassium. Thus, the membrane potential rises towards E_{Na} and then is brought back to its resting level near E_K (details have been briefly discussed recently in this Journal,⁷ and in more extended form in monographs by Hodgkin⁸ and Katz.⁹ A corresponding discussion of cardiac electrical activity can be found in Trautwein's review⁴).

In heart the initial response to excitation (depolarization, or passage of current outwards through the membrane) is a rise in sodium permeability, not unlike that just mentioned in connection with nerve and skeletal muscle. This causes the membrane potential to head toward E_{Na} . This voltage change has two results †: 1) a further increase in permeability to sodium leading to a regenerative condition ("threshold" is the depolarization at which this runaway state results); 2) a drop in potassium permeability (note the difference from other excitable membranes). The increase in sodium permeability soon decays spontaneously but, in contrast to nerve, not to resting levels. Instead, there is a slight residual elevation in P_{Na} (P in fig. 3b). What does this mean so far? The great increase in P_{Na} coupled with the fall in P_K will cause the membrane to behave very much like a sodium battery, *i.e.*, the membrane potential will rapidly approach E_{Na} . The subsequent drop in P_{Na} will cause the membrane potential to fall back somewhat (to about zero). At this point, if nothing else happened, the system would be in a steady state, *i.e.*, the permeabilities to sodium and potassium would be roughly balanced and the membrane potential would be at the value, approximately zero, associated with that balance. It is this tendency towards the existence of a steady state which leads to the "plateau" so characteristic of car-

† Both P_{Na} and P_K presumably depend on membrane structure, which in turn depends on the electrical field in which the membrane lies. Changing the voltage across the membrane changes the electrical field and apparently changes the ease with which each ion can go through the membrane. That is, both P_{Na} and P_K are "voltage-dependent."

FIG. 3. Diagram to illustrate Trautwein's summary⁴ of permeability changes underlying the cardiac action potential. *a*: scheme of the voltage changes that constitute the action potential, *i.e.*, upstroke and overshoot (*U*), plateau (*P*) and repolarization (*R*). *b* shows the initial rapid and intense (note break in scale of ordinates) transient increase in permeability to sodium during the upstroke (*U*), followed by a less intense but more prolonged residual elevation (*P*) during the plateau. With repolarization (*R*) permeability returns to resting levels. *c* shows the decrease in potassium permeability (*U*) associated with the upstroke, a low potassium permeability during the plateau (*P*) and the subsequent return (*R*) to resting levels with repolarization.



diac action potentials. § In the absence of this balance, the action potential would be over within a few milliseconds, as in nerve. Instead, the cardiac action potential persists for several hundred milliseconds. This persistence results from the presence of both a residual elevation in P_{Na} and a drop in P_K with activation.

The increase in permeability to sodium with activation can easily be divided into two parts: the rapid intense initial spike and the more

§ The term "plateau" suggests a more constant potential than is usually seen. Figure 2 shows that the "plateau" is usually not as flat as the diagram in figure 1 might suggest. Nevertheless, there still is a long phase during the action potential when the membrane potential is changing relatively slowly. This is what "plateau" is intended to imply.

prolonged but much less intense subsequent phase (see fig. 3B). It is not known whether the latter is just a less intense residual phase of the former, or whether two separate mechanisms are involved. ¶

The action potential does not stay at a pla-

¶ There is also some reason to believe that the sodium permeability falls essentially to zero and that the residual permeability during the plateau represents increased permeability to calcium. Since internal concentration of calcium ions is kept low by a specific uptake mechanism inside the cell, E_{Ca} is near E_{Na} , so an increase in P_{Ca} would behave much like an increase in P_{Na} . For simplicity we have described events in terms of increases in permeability to sodium ions only. If future experiments clearly indicate that it is only P_{Ca} which is high during the plateau, the present description will still hold if "increased P_{Ca} " is substituted for "residual increase in P_{Na} ".

teau level indefinitely. The actual recovery process is the expression of two effects: 1) a slight spontaneous tendency for repolarization; 2) an explosive regenerative process. We shall discuss these in turn. The first has not yet been characterized definitively. On the basis of the nature of membrane potentials the first stage might be expected to take one of two general forms, an instability of the mechanism determining sodium permeability such that P_{Na} drifts slightly downwards, or an instability in the potassium system leading to a slight increase in P_K . Evidence has been put forward in support of both mechanisms.¹⁰⁻¹² In addition, with recent evidence that the spike of the action potential includes a slight contribution derived from the calcium concentration cell, a third explanation involving a spontaneous decline in calcium permeability has appeared.¹² At present, we cannot assess the relative contributions of the three alternatives: it is possible that all occur. We can do little more than say that some membrane property must drift slightly during the early part of the plateau.

This drift, regardless of origin, will lead to the second stage in recovery—the regenerative phase of repolarization, with the sequence of events as follows. The drift in membrane properties leads to a slight shift of the membrane potential towards repolarization. This shift in turn leads to a slight increase in P_K . (Remember that P_K in heart muscle *fell* when the membrane potential became more positive early in the action potential. It might, therefore, be expected to rise when the membrane potential moves in the opposite direction, and it does.) This increase in P_K leads to a further repolarization of the membrane, followed by a still greater increase in P_K , more repolarization, and so on, in an explosive regenerative process. Once this phase of the repolarization is under way, it brings the membrane potential back toward resting levels very rapidly.

The terminology used in connection with the increase in sodium permeability requires some comment. With excitation P_{Na} increases, then spontaneously decreases, and cannot be made to increase to its highest possible level unless the membrane potential is first brought back to its resting level. We do not know why this is the case; this is just the way mem-

branes are made. The system behaves like a mechanism which has to be cocked by repolarization before it can be triggered. Therefore, electrophysiologists talk about a "sodium mechanism" which can be "activated" to bring about an increase in P_{Na} , and which then spontaneously becomes "inactivated" so that P_{Na} falls, and which must be "reactivated" by repolarization before it will again be possible to get a full increase in P_{Na} . It also appears that partial reactivation can occur if repolarization is not complete. In this case, a subsequent action potential may result, but the increase in P_{Na} may be less than normal. This situation will come up later when effects of drugs on overshoot potential, rate of rise of the action potential and conduction velocity are discussed.

In summary, let us go through the whole sequence of the action potential once more. With excitation there is an increase in P_{Na} so the membrane potential heads toward E_{Na} . This voltage change causes P_K to fall. The peak of the action potential is soon reached, P_{Na} falls spontaneously to a lower value, and a quasi-stable state with a membrane potential of about zero (the plateau) is reached. At this point a small instability in the membrane leads to a slow drift of the membrane potential toward the resting level. This slight change is enough, however, to initiate a regenerative cycle of increases in P_K with further repolarization, bringing the membrane rapidly back to the resting state.

PROPERTIES AND PARAMETERS

When talking about electrical activity of the heart, it is convenient to do so at several levels. Since all appear in the following discussion, they will first be listed so the reader may more easily keep them sorted out in his mind. First, effects can be classified in terms of the traditional empirical properties of automaticity, excitability and conduction. Second, corresponding to each of these properties there are measurable parameters which are used when it is desired to assign a magnitude to a change in one of the empirical properties. Examples include threshold and duration of the action potential as indices of the degree of excitability, or heart rate and slope of the pacemaker potential as measures of automaticity. Finally,

there is the underlying property of ionic permeability, which can be used to give the most unified picture of how the membrane behaves. The corresponding measurable parameters can take the form of ionic mobilities, ionic conductances, or permeability coefficients (like P_K and P_{Na}) which are all essentially variations on the same theme. For simplicity the first two forms have not been used; only the terms P_K and P_{Na} appear.

Relationships between Membrane Permeabilities and Automaticity, Excitability and Conduction Velocity

AUTOMATICITY

The action potential as described above occurs only as a result of stimulation. Clearly an additional mechanism must be responsible for the spontaneous activity seen in pacemaker cells. Its exact nature is not known. From the nature of membrane potentials, one is led to consider two principal alternatives to account for pacemaker potentials. During diastole there might be either a spontaneous decrease in permeability to potassium or an increase in permeability to sodium. The former seems more likely. (The experimental arguments¹³⁻¹⁶ are too complex to be discussed here but, fortunately, they are not essential to our survey.)

EXCITATION, INACTIVATION AND ACCOMMODATION

Excitability refers to the ability of the cell membrane to respond to stimulation (depolarization of the cell membrane or passage of outward current through the membrane) with a great increase in permeability to sodium and with the associated regenerative process of the rising phase of the action potential. Excitability is usually examined in two ways: in terms of the stimulus strength necessary to initiate a response, and in terms of the time that elapses before a second response can be elicited—the “refractory period.” Two principal factors may be considered to affect excitability: accommodation and drugs.

Accommodation

Recall that depolarization leads not only to activation of the mechanism governing P_{Na} but

also to its subsequent inactivation. The membrane can be said to “accommodate”¹⁷ to the depolarization, that is, the membrane does not fire endlessly when stimulated by a continuous current. Furthermore, a slight depolarization, which may not be enough to trigger an action potential, can lead to partial inactivation of the sodium mechanism. In other words, if the resting membrane potential does not correspond to the fully repolarized state, the sodium mechanism will probably be partly inactivated. Finally, inactivation probably begins to occur right from the beginning of the action potential. Normally, the upstroke of the action potential is so fast that negligible inactivation occurs before the action potential gets under way, but if the rate of rise is reduced, this may not be the case.

Threshold for excitation is reached when P_{Na} has increased enough so that sodium ions rush in faster than potassium ions can move out. If some inactivation has occurred, the membrane must be depolarized further before P_{Na} will be high enough to override P_K , that is, threshold will have risen or excitability will have decreased. Most stimuli depolarize rapidly so that negligible inactivation occurs before the rapid regenerative phase of depolarization is reached. However, slowly rising voltages will allow time for inactivation, with the result that the stimulus must be greater to catch a rising threshold.

Effects to be Expected When P_K and P_{Na} are Altered

P_K . An increase in P_K may be expected to hold the membrane potential more firmly near E_K and so depress excitability and slow the rate of rise of the action potential. It may be expected to hasten repolarization by pulling the membrane more strongly toward E_K . This will lead to a decrease in the duration of the refractory period, *i.e.*, the membrane will become re-excitable sooner.

P_{Na} . A decreased intensity of activation of P_{Na} will be expected to increase threshold because the membrane will have to be depolarized further before P_{Na} will override P_K .

As mentioned above, the nature of the membrane is such that, once excitation occurs and an action potential is initiated, the sodium mechanism becomes almost completely inacti-

vated and remains so until the membrane is repolarized nearly to resting levels. Conventional measurements of refractory periods amount to assessments of the degree of this reactivation of the sodium mechanism during repolarization. In turn, the duration of the action potential is an easily measured parameter reflecting electrical properties of the membrane, in particular, the refractory period (since refractory periods are roughly proportional to the duration of the action potential). But, like "excitability," "conduction velocity," and "rate of rise of the action potential" (see below), both refractory period and duration of the action potential are not fundamental parameters but rather reflections of underlying changes in P_{Na} or P_K .

CONDUCTION, CONDUCTION VELOCITY AND RATE OF RISE OF ACTION POTENTIAL

Conduction of impulses in cardiac muscle, as in other excitable tissues, is brought about by local action currents²⁻⁵; that is, the inrush of sodium ions at an active area leads to an outward current in the adjacent membrane. This outward depolarizing current is in the right direction to excite that membrane, thus, the excitation process is intrinsically self-propagating.

Conduction velocity is an expression of how fast the signal is transmitted from one point to the next, and this in turn depends on P_{Na} , i.e., on how fast the sodium enters to depolarize the membrane. If the intensity of activation of the sodium mechanism is reduced, several synergistic events result in a slowing of conduction. We shall sketch the pattern of events to indicate for the interested reader that a logical sequence exists. The sodium current rushing in will be less, so 1) less current will flow out to excite the adjacent membrane, and 2) the voltage at the point where sodium is flowing in rises more slowly. Both these effects delay excitation of the adjacent membrane. 3) Because there is a decreased intensity of current flowing out through the adjacent membrane (1, above), more time will elapse before enough current has passed through the adjacent membrane to bring it to threshold. 4) Also, because the action potential rises slowly (2, above), the outward current in the adjacent membrane will take longer

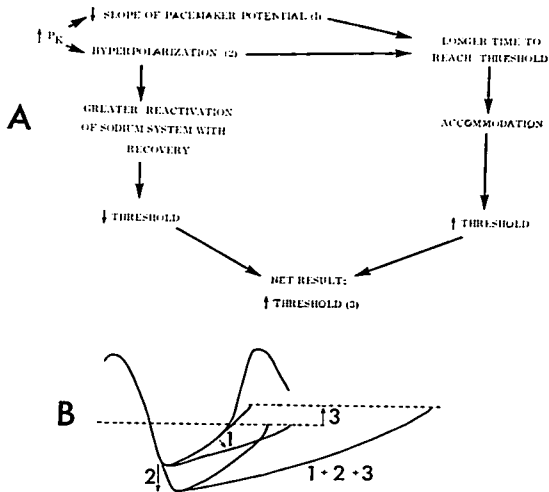
to reach values that can change that membrane potential markedly. Finally, 5) the delay is accentuated because the longer it takes to depolarize the adjacent membrane, the more time there will be for accommodation to set in there. Accommodation raises threshold and delays still further the initiation of an action potential. All these factors reinforce each other, and the overall result will be a decrease in conduction velocity.

The rate of rise of the action potential is an easily measured reflection of the electrical properties of the membrane. It is of interest in connection with conduction velocity (increased rate of rise is associated with increased conduction velocity, see above) and in connection with excitability (increased excitability is often associated with an increased rate of rise). Like conduction velocity and excitability, the rate of rise of the action potential is not a fundamental parameter, but just reflects the balance between P_{Na} and P_K . The rate of rise of the action potential will increase with an increase in intensity of activation of the sodium mechanism because sodium ions can rush in more rapidly to depolarize the membrane. Conversely, the rate of rise decreases with an increase in P_K because a stronger potassium current opposes depolarization.

These effects on P_K and P_{Na} can interact.¹⁸ For example, if the resting membrane is slightly depolarized, an increase in P_K might cause some hyperpolarization. This hyperpolarization would lead to less inactivation of the sodium mechanism, therefore to a faster rate of depolarization. On the other hand, if the increase in P_K is substantial, the membrane tends to stay near E_K and the rate of rise will be less. The final effect on the rate of rise of the action potential will depend on whether the clamping near E_K (resulting directly from the increase in P_K) is counterbalanced by the decreased inactivation of the sodium mechanism (resulting indirectly from the hyperpolarization).

The preceding discussion illustrates how a single primary event—an increase in P_K —can lead to diametrically opposite changes in an empirical measurement—an increase or decrease in rate of rise of the action potential—depending on the initial state of the membrane. Such a viewpoint will be helpful when we try

FIG. 4. A: scheme to indicate interplay of factors governing heart rate. B: diagram to illustrate the three alterations that can be associated with a decrease in automaticity. The slope of the pacemaker potential can decrease (1) so it takes longer to reach threshold (dotted line in B). The cell can hyperpolarize further in diastole (2) so it has further to go to reach threshold. Or the threshold itself can rise (3) and, therefore, take longer to reach. All three occur with acetylcholine (1 + 2 + 3 in B).



to fit all the effects of acetylcholine into a coherent pattern.

Action of Drugs

ACETYLCHOLINE

We now indicate how all the actions of acetylcholine on electrical behavior of cardiac muscle can be tied to a *single* underlying action on the membrane—an increase in the permeability to potassium (increase in P_K). The task is not so hard as it may seem. To illustrate, we consider a list of known effects of acetylcholine and show how these would be expected to result from an increase in P_K .

1) *Resting membrane potential.* This is found to hyperpolarize if not near E_K , otherwise not to change much. An increase in P_K will clearly lead to further polarization (*i.e.*, the membrane potential will shift closer to E_K) if not already near E_K .

2) *Pacemaker potential (heart rate).* With an increase in P_K the mechanisms responsible for spontaneous depolarization will be opposed by a greater tendency for the membrane potential to stay at its resting level. In other words, the spontaneous process will have to

continue longer to reach threshold, *i.e.*, beats will occur at greater intervals—the heart rate will slow. In addition, if there is any hyperpolarization (see comments above on resting potential) the spontaneous depolarization will have further to go to reach threshold. Finally, the threshold potential may be more positive because there will have been more time for accommodation to set in. (If the increase in P_K produced some hyperpolarization, more complete reactivation of the sodium mechanism will result. This would tend to oppose accommodation. It is hard to say *a priori* which effect would win out; it turns out that the accommodation does.) Thus, acetylcholine decreases the heart rate for three reasons: the slope of the pacemaker potential is more negative, and threshold potential is more positive. These factors are indicated in figure 4A, and the final result is indicated diagrammatically in 4B.

3) *Duration of action potential.* Refractory period. An increase in P_K can be expected to drag the membrane potential back to its resting level sooner. In other words, the increase in P_K induced by acetylcholine acts synergistically with the increase in P_K normally re-

sponsible for repolarization. The more rapid return to the resting membrane potential appears as a briefer action potential, making possible an earlier recovery of excitability. This will appear as a briefer refractory period.

4) *Overshoot potential.* The potential reached at the peak of the action potential reflects the balance between peak sodium permeability and potassium permeability. An increase in the latter with acetylcholine will tip the balance toward E_K so the overshoot potential will be smaller.

5) *Conduction velocity.* Here, we come to a more complicated situation, because three effects are possible and have been seen. Conduction velocity may increase, decrease, or not change.⁴⁻⁶ We shall discuss each situation in turn. i) If the resting membrane potential were originally some distance positive to E_K , i.e., slightly depolarized, and the increase in P_K were not very large, conduction velocity might be expected to increase with acetylcholine. The reason is that a slight increase in P_K would lead to hyperpolarization, which would be associated with more complete reactivation of the sodium mechanism responsible for the upstroke of the action potential. (Remember that with depolarization P_{Na} rose and the *fell* spontaneously. To return the membrane to a state in which P_{Na} can again be turned on fully, the membrane must be repolarized completely. The hyperpolarization resulting from the increase in P_K would just finish the job.) As a result, when the membrane is excited a larger increase in P_{Na} would be possible, a greater sodium current would rush in to depolarize the membrane more rapidly, and, therefore, the conduction velocity would increase. ii) Next, suppose the membrane potential were already at E_K before the acetylcholine was added. The sodium mechanism would already be fully reactivated. So the only effect of an increase in P_K will be to oppose depolarization—i.e., to slow the rate of depolarization. iii) Finally, a combination of the above situations would occur when the membrane is not at E_K , but the increase in P_K is moderate. Both the previous two factors would operate. There would be some reactivation of the sodium mechanism and, opposing it, the increased tendency to stay at E_K . As P_K became larger and larger, decrease in con-

duction velocity should be more likely. It is reasonable to expect that an occasional worker might have studied a cell with a membrane potential and an increase in P_K such that he found a negligible change in conduction velocity. In this case, the two effects, greater reactivation and “clamping” at E_K , would have happened to balance.

Although the above line of reasoning is straightforward, it is cumbersome. The scheme in figure 5 may help to indicate the pattern more explicitly.

6) *Atrioventricular conduction.* Cells in the atrioventricular node have action potentials which differ considerably from those in the rest of the heart¹⁹ (see fig. 2, I-P). In particular, they rise from a less negative resting membrane potential and have a lower amplitude. Quite often they show steps on the rising phase, a feature quite suggestive of spatial summation. These cells have not been investigated very thoroughly, so one cannot say for sure what to expect from an increase in P_K (nor even say that acetylcholine increases P_K in these cells). However, the known effects of acetylcholine of increasing the refractory period of the atrioventricular node and increasing the delay in the conduction of impulses from atrium to ventricle can be made to fit plausibly into the general scheme. To do so we suppose either that the low resting membrane potential implies E_K is relatively positive in atrioventricular cells or that the low amplitude and very slow rising phase of the action potential implies that sodium activation is never great in these cells.** In either case, an increase in P_K with acetylcholine would be expected to lead to a slower rate of rise of the action potential. Since the rising phase accounts for a large fraction of

** In fact, it is tempting to suggest (see also Paes de Carvalho et al.²⁰) that the characteristic features of atrioventricular nodal cells might be attributable at least partly to a weaker mechanism for the rapid and intense increase in P_{Na} seen with activation in other excitable membranes. In other words, the initial brief spike, I in curve B of figure 3, might be so attenuated that activation leads mainly to the small increase in P_{Na} seen during the plateau in other cells of the heart. If this were the case, the action potential would rise much more slowly (as it does) because sodium ions would not rush in rapidly to depolarize the membrane, and the peak of the action potential would be near zero—i.e., at the plateau level (where it is).

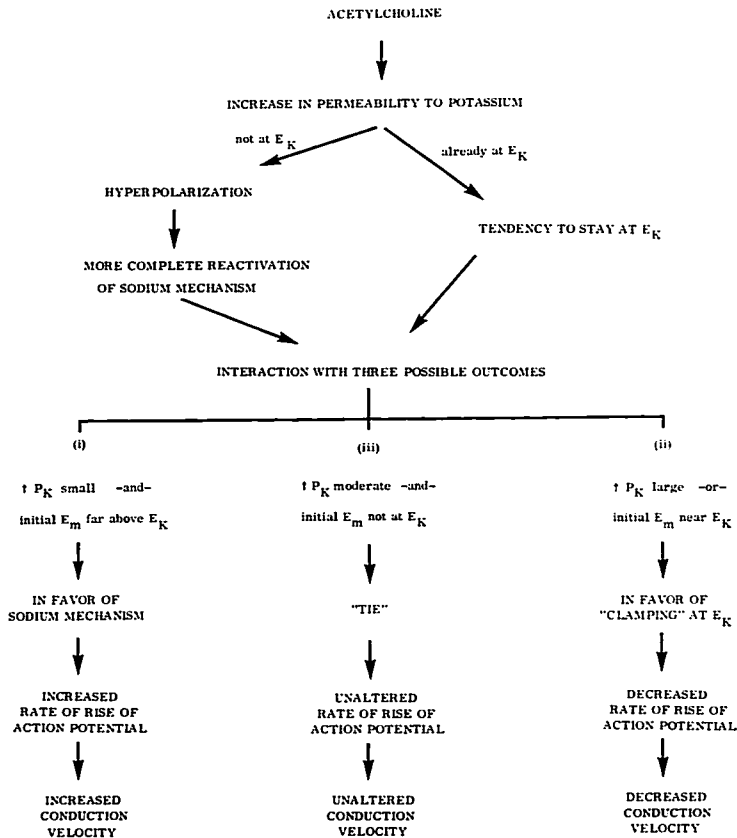


FIG. 5. Scheme to show interplay of factors involved in the action of acetylcholine on conduction velocity. All effects stem from an increase in P_K . Conduction velocity may increase, decrease or not change.

the duration of the action potential in atrioventricular nodal cells, especially in the lower node, a longer action potential results. Therefore, the refractory period will increase. Furthermore, the slower rate of rise leads to delayed passage of the signal through the node and, therefore, to an increased P-R interval.

In summary, it is possible to fit the observed

effects of acetylcholine into a general pattern without much difficulty (except in the case of the atrioventricular node, where we just do not yet have enough experimental results to argue strongly). We realize that solid experimental support is absent in some places, but we feel that the overall picture is worth presenting, both as an approach to looking at the

action of acetylcholine and because we feel it unlikely that it will prove inaccurate in any major respect.

EPINEPHRINE

Unfortunately, with the sympathomimetic amines experimental progress is much less advanced than with acetylcholine. We know the actions at the descriptive level (epinephrine accelerates the pacemaker, speeds conduction, etc.) but the actions on membrane permeabilities have not yet been worked out. For example, the mechanism by which epinephrine increases the slope of the pacemaker potential appears to involve an effect on a spontaneous decrease in the permeability to potassium which occurs during diastole,¹³ but the argument is not strong.

ANTIARRHYTHMIC DRUGS

Quinidine will be taken as the prototype because it has been studied most extensively. Procainamide,²¹ lidocaine (Xylocaine),²² and propranolol (Inderal)²³ appear to behave similarly. Diphenylhydantoin (Dilantin) is the odd-man-out (see below).

The actions of quinidine on excitable membranes all seem to stem from an effect on sodium permeability. In the presence of quinidine, excitation leads to less increase in sodium permeability than normally seen. The known actions of quinidine follow directly. A reduced increase in sodium permeability means that the action potential rises less rapidly and overshoots less. This is observed.^{24, 25} It also means that conduction velocity will be reduced. This, too, is seen.²⁵ Finally, decreased excitability is to be expected; more depolarization is required to increase the sodium permeability to a point (threshold) at which the regenerative mechanism takes over. At the other end of the action potential, repolarization will have to proceed further before the sodium mechanism becomes sufficiently "recocked" to allow a subsequent action potential to be generated, *i.e.*, the effective refractory period will be prolonged.²⁴⁻²⁶ From a quantitative point of view, the effect of a given reduction in sodium permeability will be to cause a greater proportional change in the rate of rise of the action potential and in conduction velocity than in the duration of refractory period. Re-

polarization is reasonably rapid so little additional time is required in the presence of quinidine. Therefore, as pointed out by Vaughan Williams,²⁴ the therapeutic efficacy of quinidine is more likely to be related to the reduction of rate of rise of the action potential than to the increase in refractory period.

Quinidine does not appreciably alter the resting membrane potential because its action is on the *increase* in sodium permeability with activation, not on resting sodium permeability. Quinidine has essentially no effect on the duration of the action potential because duration is determined by the nature of the regenerative process associated with repolarization. This occurs long after the quinidine-sensitive phase of intense increase in sodium permeability is past.

Diphenylhydantoin does not behave like quinidine. It increases the rate of rise of the action potential,²⁷ presumably by *increasing* the degree of activation of sodium permeability seen with excitation.

This leads to a final point in connection with antiarrhythmic agents. Starting from the common denominator of an effect on sodium permeability, we can tie in observed effects on measurable electrical parameters such as conduction velocity. When we try to take the next step, that is, to relate these actions to the therapeutic effect of antiarrhythmic agents, success cannot be expected until the pathophysiology of arrhythmias is understood. In other words, one cannot say which property of the membrane should be corrected to restore normal rhythm. The clinical use of these agents can be only empirical at present, and the therapeutic efficacy of diphenylhydantoin only serves to emphasize the truth of this. Certainly, the appearance of an agent which is effective but which has an action diametrically opposite to that of quinidine, while fascinating, is not entirely surprising. It certainly does not invalidate the argument for describing events in terms of membrane permeabilities. It may mean simply that there are several ways to antagonize the process responsible for the arrhythmia. For example, one could argue *post hoc* that decreasing sodium permeability would decrease excitability and antagonize initiation of extraneous responses, and that an increase in sodium permeability

could, by increasing conduction velocity, lead to the arrival of an incoming abnormal signal before excitability had recovered. Clearly the best position to take at present is to recognize that the limiting factor in understanding the action of antiarrhythmic agents is our ignorance of the nature of the arrhythmias themselves.

CARDIAC GLYCOSIDES

The electrical \ddagger effects of cardiac glycosides are complex because both direct and indirect components are involved. It is still tempting to picture all the direct effects as the result of one membrane action—less increase of P_{Na} with activation—then to superimpose the indirect effects. The decreased rate of rise of membrane potential expected with a decrease in P_{Na} is observed experimentally. Interference with the sodium mechanism is a reasonable basis for the observed decrease in excitability and interference with atrioventricular conduction.^{29,30} The extravagal action³¹ of cardiac glycosides on atrioventricular conduction would then correspond to the diminished increase in P_{Na} with activation. The indirect “vagal” effect is explained by superimposing the increase in P_K caused by vagal release of acetylcholine. The direct decrease in P_{Na} and indirect increase in P_K would be synergistic as required.

An inconsistency in this whole outlook comes in the consideration of the increased ventricular automaticity (expressed as ventricular extrasystoles, ventricular tachycardia, or ventricular fibrillation) of toxic levels of cardiac glycosides. However, a solution is indicated by experiments on dogs whose hearts have had the sympathetic innervation destroyed. With overdoses of cardiac glycosides these animals do not die in ventricular fibrillation; their

\ddagger The inhibitory action of cardiac glycosides on the sodium pump is well known. However, the sodium pump serves primarily to “charge” the membrane battery by maintaining ionic electrochemical gradients, but does not participate directly in the membrane permeability changes that constitute the action potential itself. For simplicity, therefore, actions on the pump will not be included in the present discussion. Some effects of altered ionic gradients on electrical activity must be expected to follow interference with the pump mechanism but these can be treated as second-order effects and neglected in a qualitative approach such as that presented here.

hearts just become inexcitable.³² Apparently, sympathomimetic amines participate in the increased automaticity seen in innervated hearts. This is reasonable, for sympathomimetic amines are known to accelerate pacemaker activity in all parts of the heart. The inexcitability seen in denervated hearts can be expected from interference with activation of the sodium mechanism produced directly by the cardiac glycosides. Thus, the toxic actions of the cardiac glycosides can be pictured as the net result of 1) a decrease in excitability resulting from interference with activation of the sodium mechanism—a *direct* effect of the cardiac glycoside, and 2) an increase in automaticity mediated *indirectly* by endogenous sympathomimetic amines (no information is available to explain how the cardiac glycosides bring about this indirect effect). The second of the two effects normally predominates; the first effect is revealed only in denervated hearts from which the second has been removed. Incidentally, the indirect chronotropic action is probably opposed somewhat by the cardiac glycosides; these drugs have inhibitory action on the chronotropic actions of epinephrine.^{32,33} So, again, it is possible to fit together a plausible picture of the action of a class of drugs by centering on one basic action on the membrane. More experimental evidence elucidating specific points is needed, but even in its absence a unified picture is emerging.

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Drugs

CARDIOVASCULAR RESPONSE TO MORPHINE The cardiovascular responses to intravenous morphine, 1 mg/kg body weight, were compared in seven patients with aortic-valve disease and eight without major cardiac or pulmonary disease. The control pulse rates were higher and the control stroke indexes lower in the patients with cardiac disease. Following administration of morphine, significant increases in cardiac index, stroke index, central venous pressure and pulmonary arterial pressure occurred in the cardiac-disease patients but not in other patients. These observations suggest that large doses of morphine may be used with safety in patients with minimal hemodynamic reserves. (*Lowenstein, E., and others: Cardiovascular Response to Large Doses of Intravenous Morphine in Man, New Engl. J. Med.* 281: 1389 (Dec.) 1969.)