

The Nature of "Depolarization Block"

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SINCE THE WORK of Burns and Paton¹ was published, neuromuscular blocking agents have been classified as competitive and "depolarizing." The mechanism of action of the competitive agents, tubocurarine or gallamine for example, is straightforward; it is a pharmacologic competitive antagonism.

The depolarizing agents are said to block "by depolarization." This is not very meaningful, since the transmitter, acetylcholine, stimulates by depolarization. Burns and Paton indicated the true nature of the block ("the excitability of the membrane adjacent to the end-plate falls"), but an explicit analysis of the overall process in the light of modern views of the physiology of excitable membranes is not available. Standard textbooks are not much help. McIntyre² says simply, "the junctional tissue of the muscle sole plate is held in a depolarized state, and consequently transmission fails." Koelle³ refers to Burns and Paton, but simply says that "C10 produces an immediate and persisting depolarization of the end-plate and the adjacent area of the sarco-plasmic membrane." The exact mechanism cannot be dismissed so briefly.

The following discussion will first review the aspects of electrophysiology relevant to the action of decamethonium and then describe the nature of depolarization block in detail. Tubocurarine and decamethonium will be used as examples of typical competitive and depolarizing neuromuscular blocking agents.

It is convenient to analyze electrophysiologic phenomena in terms of changes in the trans-

membrane potentials of nerve or muscle cells. These can be recorded directly with intracellular electrodes, but when this is done in muscle a contraction may destroy the cell, electrode or both. With muscle, therefore, extracellular recording must often be used and the change in transmembrane potential inferred indirectly. For purposes of clarity in this paper, events will often be described as if an intracellular electrode were used. Some of the figures (10, for example) will be diagrammatic so the time course illustrated may not be exact. Nevertheless, the general pattern will be representative of the actual physiologic event. As will become apparent, the overall process is complicated enough without the discussion of variations in experimental techniques.

The Nature of the Muscle Membrane

To understand the action of decamethonium, one must recognize that the cell membrane of a muscle cell is not homogeneous. There is a chemically excitable membrane at the motor endplate region where the transmitter acts. Incidentally, this area is not electrically excitable.⁴ The remainder of the membrane is electrically excitable, but does not normally respond to drugs.⁵ Before a review of the properties of each type of membrane, a discussion of concentration cells will be useful, as models for the processes determining membrane potentials.

Concentration Cells and Membrane Potentials

Suppose a membrane, impermeable to chloride but not to potassium ions, separates two different solutions of potassium chloride (fig. 1a). Because of the concentration gradient both potassium and chloride ions will try to flow from the concentrated to the more dilute solution. However, because the membrane

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Accepted for publication February 28, 1968. The author is supported by a Career Development Award (NB-25,952) and a Research Grant (NB-04168) from the National Institute of Neurological Diseases and Blindness.

will not let chloride ions through, only potassium ions will actually cross the membrane. An excess of potassium ions will build up on the side where the solution is more dilute. This excess of positive charges will lead to a positivity on that side. This electrical effect will increase as more potassium ions cross the membrane until the voltage difference between solutions becomes great enough to be equal (and opposite) to the concentration gradient driving potassium across the membrane. At this point there will no longer be any net driving force on the potassium ions and an electrochemical equilibrium will exist. The original concentration difference will lead to a voltage difference across the membrane. The voltage to be expected can be predicted from thermodynamics (Nernst equation), but need not concern us here. Typically only a very few potassium ions actually have to cross the membrane for there to be enough separation of charge to produce the voltage difference.

Now consider a slightly more complicated model (fig. 1b) where the concentrations have been chosen to approximate those found inside and outside of excitable cells (cf. Katz,⁶ p. 43, frog muscle). Suppose first that the membrane is permeable just to potassium. Then, by the process just described, the inside would become negative. Next, suppose it is permeable only to sodium. Then the inside would become positive. Finally, suppose the membrane is very permeable to potassium and only slightly permeable to sodium. The inside can be expected to become negative, but not so negative as when there is no permeability at all to sodium. Thus, a scale exists (fig. 2) for possible membrane potentials (inside potential relative to outside); at one extreme the inside will be about 100 mV. negative, and at the other, about 75 mV. positive. These extremes represent the values to be expected if the cell were behaving like a pure potassium battery or a pure sodium battery. These values are called E_K and E_{Na} . The actual resting membrane potential found in muscle cells is about -90 mV., indicating that the cell behaves mainly like a potassium battery with a slight resting permeability to sodium. That is, the membrane potential is determined by the relative permeabilities to the ions distributed across it.

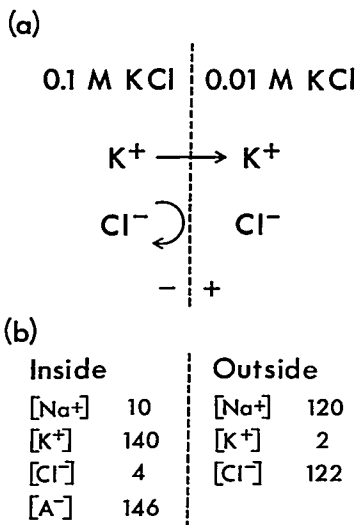


FIG. 1a. A hypothetical concentration cell. If the membrane is permeable to potassium, but not to chloride ions, the side where the potassium chloride is more concentrated will become negative. b. Another concentration cell. Ion concentrations (millimolar) on each side chosen to mimic those found inside and around excitable cells (frog muscle cells specifically). A⁻ represents nondiffusible intracellular anions.

The membrane is also permeable to chloride; however, the concentrations of chloride are such that $E_{Cl} \approx E_K$, so for the present discussions we may ignore chloride.

The cell described will run down if left alone. Running down is prevented by the sodium pump, which ejects sodium that leaks in and maintains the potassium concentration gradient (the exact way the sodium pump moves potassium need not concern us here). The sodium pump will not be involved in the following discussion except in its role of keeping the "battery" charged. All voltage changes produced are brought about by changes in the membrane permeability, so that the membrane potential becomes governed by E_{Na} or E_K in different proportions.

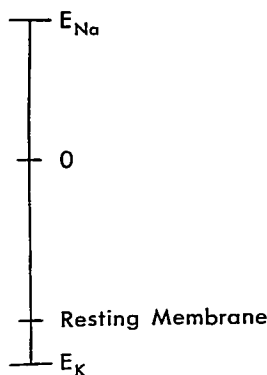


FIG. 2. Voltage scale indicating possible values membrane potential might assume.

An Aside on Permeability

Permeability of membranes to ions plays a central role in electrical behavior of membranes. Permeability can be expressed in many ways, all of which are related. One can talk about the *mobility* of potassium in the membrane (u_K). This is defined in terms of how fast (cm./sec.) the ion would move through the substance of the membrane in a given voltage gradient. Alternatively, one can modify

the mobility somewhat so as to put it into a form more convenient for use with membranes and talk about a permeability coefficient (P_K) of the membrane to potassium.

$$\left(P_K \text{ is } \frac{RT}{F} \cdot u_K \right)$$

membrane-water partition coefficient,
thickness of the membrane

cf. Hodgkin and Katz,⁷ p. 75).

Both u_K and P_K are phrased in terms of the physicochemical properties of the membrane. However, electrical properties are often measured, and it is convenient to talk in terms of electrical parameters such as resistance or conductance. The reader, therefore, will encounter terms like R_m , the *membrane resistance* or g_m ($= 1/R_m$) the *membrane conductance*; of particular importance is the *potassium or sodium conductance*, which is that portion of the membrane conductance attributable to flow of potassium or sodium ions.

Finally, two types of "conductance" may appear, the *slope conductance* and the *chord conductance*. The slope conductance is dI/dV , that is, the incremental increase in current (I) for a small increase in voltage. (One could measure this by passing a small current through the membrane and measuring the re-

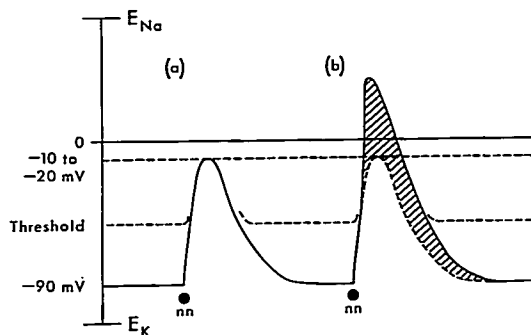


FIG. 3a. The endplate potential. The membrane seeks an equilibrium level of about -10 to -20 mV, and then returns to its resting value as the transmitter's action ceases. *b*. Solid line is the electrical response seen at the endplate region following nerve stimulation (nn). The effect of an action potential is superimposed (shaded area) on an endplate potential like that of *a*. (The broken line, labeled threshold, indicates the degree of depolarization required to initiate an action potential in the membrane adjacent to the endplate.

An upward displacement of this line implies accommodation. At the start of the action potential the line representing threshold has been drawn to show a rise, and then a gap has been left, since the term threshold is not very meaningful during the action potential.)

sultant change in membrane potential.) The chord conductance is invoked when flow of a given ion is to be predicted from the membrane potential. Chord conductance to potassium (g_K), for example, takes the form $g_K = I_K / (V_m - E_K)$. The nature of this definition is clearer if the equation is rewritten $I_K = g_K (V_m - E_K)$. This form indicates that from a knowledge of g_K and the difference between the membrane potential (V_m) and the potassium equilibrium potential (E_K) one can get the flow of potassium ions across the membrane. The exact relation of conductance to mobility in the membrane is much less simple than in the case of permeability. In fact, the relationship depends on the specific model of the membrane one chooses. However, for any given model the relationship will exist, so one can regard the conductance as derivable, in principle at least, from the mobility.

The potassium or sodium chord conductance (g_K or g_{Na}) is actually what is measured in electrical experiments intended to measure the permeability of the membrane and so will be used throughout this discussion as the measure of permeability of the membrane to the ions. The important point is that all these indices are just measures of the ease with which an ion can get through a membrane.

The Action of the Transmitter

Nerve stimulation leads to the release of acetylcholine, which diffuses across the synaptic cleft to react with specialized sites (receptors) on the surface of the muscle endplate. As a result of this reaction, the membrane of the endplate region alters its properties. Instead of being very permeable to potassium (high " g_K ") and only slightly permeable to sodium (low " g_{Na} ") as in the resting state, it becomes very permeable to both.⁸ It, therefore, behaves like a battery with a voltage halfway between E_K and E_{Na} . If the resulting voltage change—the endplate potential—could be seen uncomplicated by the action potential it normally triggers, a curve such as that of figure 3a would be seen. In fact, as soon as the endplate potential depolarizes the muscle membrane to about -70 mV., an action potential is produced and a combination of endplate potential plus action potential (*cf.* del Castillo and Katz⁹) is seen. A schematic representation

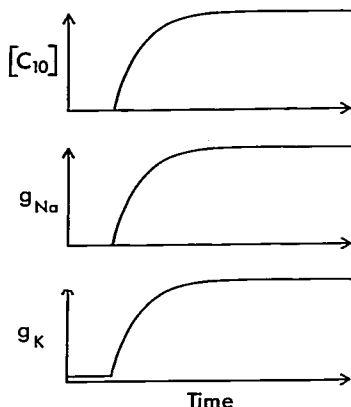


FIG. 4. The action of decamethonium. As long as the endplate is exposed to decamethonium, the conductance to sodium (g_{Na}) and to potassium (g_K) are elevated. (The degree of elevation will increase with increasing doses of decamethonium.)

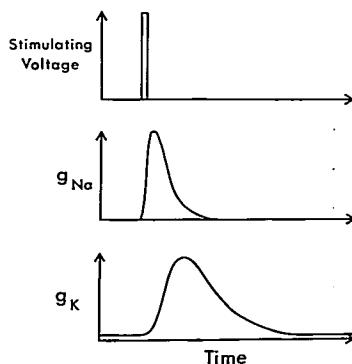


FIG. 5. Membrane changes associated with the action potential. g_{Na} = conductance of cell membrane to sodium; g_K = conductance of cell membrane to potassium (after Hodgkin).

is shown in figure 3b. The endplate potentials are brief because the transmitter is rapidly broken down by cholinesterase.

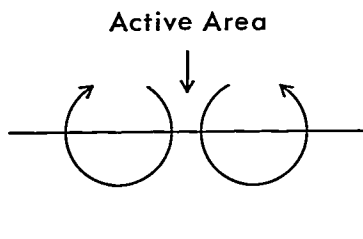


FIG. 6. Local action circuits. Current flowing inward at one part of the membrane must flow out elsewhere (after Hodgkin).

The Action of Decamethonium at the Endplate

As Burns and Paton have pointed out, decamethonium acts identically to acetylcholine. It differs only in that it is not broken down by cholinesterase and so can produce a prolonged effect. The action of decamethonium can be described by a diagram such as that of figure 4. As long as the concentration of decamethonium is maintained at the endplate region, there will be an increased permeability of the endplate membrane to sodium and to potassium.

The Nature of an Action Potential in Nerve or in the Electrically-excitable Membrane of Muscle

We turn now from chemically-excitable membrane to electrically-excitable membrane. It has long been known that the passage of the signal along a nerve was associated with an electrical change—the action potential. With the advent of techniques for directly recording and controlling the membrane potential, a detailed picture of the action potential has emerged. In particular, the model of Hodgkin and Huxley¹⁰ gives us a solid basis for picturing nervous events. Hodgkin and Huxley attribute the action potential to (i) a transient large increase in permeability of the membrane to sodium, followed by (ii) a delayed increase in permeability to potassium (above even the high resting level). As a result of the first change (increased g_{Na} so that $g_{Na} \gg g_K$) the membrane will no longer behave like a potassium battery, but rather like

a sodium battery, so that the membrane potential will shift to a state where the inside of the cell becomes positive. The fact that this increase in g_{Na} is transient means that the inside of the cell will be positive for only a short time and the cell membrane will soon (in milliseconds) start to head back to its normal state of behaving like a potassium battery. The delayed increase in permeability to potassium just accelerates this return. (Incidentally, this process typically carries the membrane potential closer to E_K than the resting potential. This is the reason for “after-potentials.”)

This complex sequence of events is triggered by depolarization of the membrane. Hodgkin and Huxley put an electrode in the center of a nerve fiber and, with an electronic circuit, forced (“voltage clamp”) the membrane potential from its normal resting state to a state where it was less negative inside. They summarize the subsequent events by a diagram such as that of figure 5. As the membrane potential returns to normal following the peak of the action potential (which would occur just after the peak in the g_{Na} curve), the delayed increase in permeability to potassium is turned off and the mechanism associated with the transient increase in permeability to sodium is reset. Figure 5 can serve as a basis for a mental picture of what goes on during excitation in electrically-excitable nerve or muscle membrane.

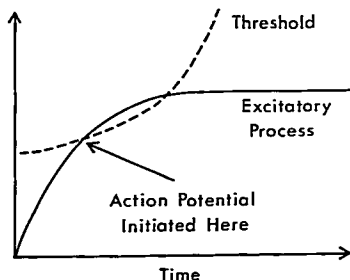


FIG. 7. Excitation and accommodation in electrically excitable membranes. When current is passed through a membrane to excite it, the threshold (broken line) rises (after Hill).

Local Action Currents

How does the action potential propagate? To start the process the membrane must be depolarized. In studies with giant nerve cells this can be done by "injecting" positive ions directly into the cell interior. In normal nerve transmission the same sort of process occurs. However, it is the activity associated with the action potential which does the "injecting." When the g_{Na} is very high, sodium ions rush into the cell (because the membrane no longer resists their flow and they are being driven by both a concentration and an electrical gradient). This inrush of sodium ions far overrides the resting outflow of potassium, so there is a net flow of positive charges into the cell interior. Now from physics we know that electricity cannot pile up appreciably at a point, so this positive current must flow axially into the core of the adjacent part of the cell which has not yet become active. From here it passes out through the membrane (fig. 6) to complete the circuit. This current flow will make this area of the cell less negative inside; that is, it will depolarize this part of the cell membrane and initiate an action potential there. This activity will in turn activate the next segment of the cell membrane so the active process is self-propagating. Diagrammatically, this mechanism whereby the inrush of sodium ions in one segment of the axon leads to depolarization of the adjacent membrane is represented by drawing small circuits, "local action currents" as in figure 6. This sort of diagram just emphasizes that a closed circular path must describe the currents flowing. As was noted in the discussion of concentration cells, very few sodium ions must enter the cell to produce the voltage change which is the action potential. The internal concentration of sodium is affected negligibly by this small addition of sodium.

Alternatively, one may simply say that when the membrane is depolarized at one point, the depolarization will spread somewhat and drag the membrane potential in an adjacent segment of membrane away from its resting level to threshold.

Threshold

It is possible to depolarize the membrane slightly and not lead to the regenerative proc-

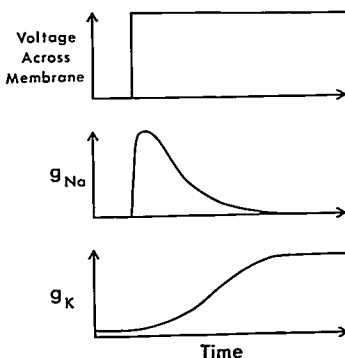


FIG. 8. Effect of a prolonged depolarization on membrane properties of an electrically-excitable membrane. Symbols as in figure 5 (after Hodgkin).

ess of the action potential. A small depolarization will lead to a slight transient increase in permeability to sodium, but not enough to override the tendency of the resting membrane to behave like a potassium battery.

However, there is a degree of depolarization that will lead to enough increase in permeability to sodium that the tendency to behave like a sodium battery will become predominant. The membrane will continue to depolarize and will, therefore, behave still more like a sodium battery. This will make it depolarize still more and an explosive, regenerative process occurs leading to the full-fledged all-or-none response of the action potential. The level to which the membrane had to be depolarized to get it into the runaway state is called the threshold.

Accommodation

We come now to the phenomenon which is the basis of the neuromuscular block produced by decamethonium. Hill¹¹ has pointed out that when stimulating electrodes are put on a nerve and current is passed through the nerve, not only is the *excitatory process* (the action potential just described) initiated, but also a second process—*accommodation*—occurs, and leads to a state of inexcitability of the electrically-excitable membrane. Hill pictures events

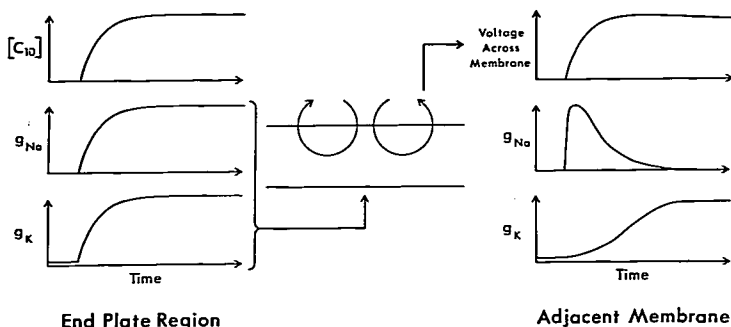


Fig. 9. Summary of the action of decamethonium. Left side indicates action at endplate to produce depolarization. In the electrically-excitable membrane this produces the voltage change indicated at the top of the right side of the figure. This voltage change, in turn, produces the permeability changes indicated below, leading to a state of accommodation.

diagrammatically as in figure 7. If a steady current is passed through a muscle the electrical changes (solid line) in the membrane reach threshold (and lead to an action potential), but also the threshold (broken line) rises. If the electrical shock is fast enough, the excitatory process reaches threshold before the threshold rises out of reach. However, because the current is passed steadily through the nerve, a state is quickly attained where the threshold has risen beyond the reach of the excitatory process. In this state the membrane is inexcitable or refractory—it is “accommodated.” Hill’s diagrammatic representation of the phenomenon is still very useful, and will be retained in the present discussion (for example, figure 10).

Accommodation occurs to different degrees in different types of electrically-excitable membranes. At one end of a spectrum is the ordinary nerve fiber which accommodates very rapidly, while at the other end is the nerve membrane adjacent to a sensory ending. This type of membrane fires repetitively when depolarized by the generator potential (a steady depolarization of the nerve ending produced by the relevant sensory stimulus). In fact, the rate of repetitive generation of action potentials is the measure of the intensity of the stimulus. Clearly, accommodation must occur much less in this second type of nerve. The

electrically-excitable membrane of muscle lies in the spectrum close to the end typified by ordinary nerve fibers; that is, muscle membrane accommodates rapidly. For ease of description in what follows, it will be treated as if it is fully accommodated after the initiation of one impulse. This is overstating the case slightly, but will not affect the general picture.

It is also possible to view accommodation in the light of Hodgkin and Huxley’s model. If an electrically-excitable membrane is depolarized and held depolarized, one sees initially the transient increase in permeability to sodium, and the potassium permeability rises after a short delay (i.e., the normal mechanisms associated with an action potential occur). However, because the membrane is artificially kept in a depolarized state, even the high g_K cannot bring the membrane back to its resting state. It seems that unless this is done the mechanism by which g_{Na} increases on depolarization is inactivated. One might say that the sodium mechanism has to be “re-cocked” by a return of the membrane potential to its resting level. With a persistent depolarization of an electrically excitable membrane, therefore, one ends up in a state (of “accommodation”) where (i) the sodium mechanism is inactivated and (ii) the potassium permeability is even higher than the resting level. For both these reasons the membrane will be

inexcitable. Figure 8 indicates the changes in an electrically-excitabile membrane which is depolarized for more than a brief period.

Figure 4 serves as our model of what happens when a constant chemical stimulus is applied to a chemically-excitabile membrane and figure 8 as the model when a constant electrical stimulus is applied to an electrically-excitabile membrane.

The Nature of Depolarization Neuro-muscular Block

The electrophysiologic notions just described allow us to describe the actions of decamethonium in a straightforward fashion. When demamethonium is applied it acts to depolarize the endplate region of the muscle membrane. This depolarization, by the mechanism discussed under "local action currents," leads to depolarization of the adjacent *electrically-excitabile* muscle membrane. Initially an action potential will be produced, as with the action of the transmitter. But, because the decamethonium is not broken down, the depolarization of the endplate region will persist so the adjacent electrically-excitabile membrane will be kept depolarized, too. It will,

therefore, be in a situation similar to that illustrated by figure 8. It will not be an identical situation in that figure 8 illustrates an experiment in which the membrane is kept exactly at one level of depolarization, whereas with decamethonium the delayed increase in permeability to potassium will counteract somewhat the depolarizing effect of the adjacent endplate. In any event, the continuous action of decamethonium leads to the existence of an area of accommodation and, therefore, of inexcitable membrane around the endplate. Figure 9 gives a scheme indicating the overall process.

If the nerve is stimulated during the persistent depolarization of decamethonium, the acetylcholine may lead to a slight further depolarization on top of that due to the decamethonium, but this endplate potential will not be able to excite the adjacent membrane. The passage of information from the nerve to the contractile mechanism of muscle is blocked. The block is *not at the endplate* (it is responding quite adequately with a depolarization). The block is at the next stage; no action potential can be produced in the adjacent, electrically-excitabile membrane.

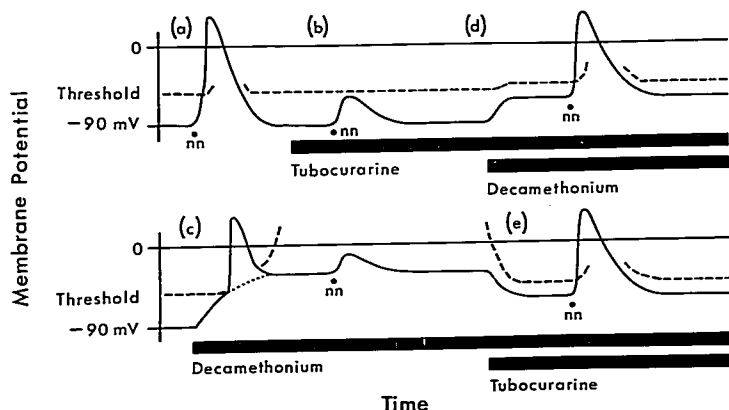
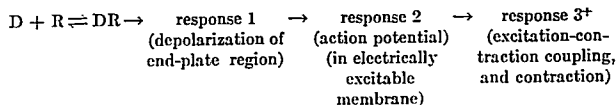
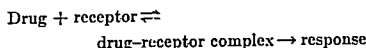


FIG. 10. Schematic representation of the actions and interactions of drugs at the neuromuscular junction. Ordinates = membrane potential as if recorded by an intracellular micro-electrode. Abscissa = time. Solid line = membrane potential. Broken line = threshold. nn indicates nerve stimulation. See text for description.

Usually in pharmacology one pictures:



The block with decamethonium is at the level of "response 2."

Schematic Representation of the Actions of Drugs at the Neuromuscular Junction

The actions and interactions of many drugs at the neuromuscular junction can be pictured by imagining a microelectrode were put into the endplate region and electrical changes were recorded even during a twitch (which in an actual experiment would probably break the electrode and/or the cell membrane).

ACTION OF THE TRANSMITTER (THE "ENDPLATE POTENTIAL")

In figure 10a the action of a brief pulse of acetylcholine is pictured. First imagine the microelectrode is inserted and the -90 mV. negativity of the cell interior is recorded. Next, the nerve is stimulated (at nn). The membrane potential heads toward a value of about -10 to -20 mV. (*cf.* Katz,⁶ chapter 8). However, before it gets there it reaches threshold (broken line), and an action potential is generated in the adjacent electrically-excitable membrane. The electrical changes associated with this action potential obscure the subsequent course of the endplate potential (which follows a course illustrated by the dotted line in figure 3b).

ACTION OF TUBOCURARINE

Tubocurarine will react with the endplate receptors, but will cause no permeability change by itself. Therefore, as indicated in figure 10b, no electrical change will be seen. If, now, the nerve is stimulated, the transmitter released will find a considerable fraction of the receptor pool occluded by tubo-

In the case of agents acting at the neuromuscular junction this situation still holds, but it should be recognized that the scheme should be put more explicitly:

curarine molecules. Therefore, less increase in permeability to potassium and to sodium will be produced. Only a small depolarization of the endplate will result, threshold will not be reached, and neuromuscular block will occur.

ACTION OF DECAMETHONIUM

As indicated in figure 10c, when decamethonium is administered the endplate region will be depolarized and an action potential will be generated in the adjacent, electrically-excitable membrane. However, when the events of the first action potential have worn off, the membrane potential will not return to -90 mV because the decamethonium is still acting to keep the whole endplate region and adjacent membrane depolarized. Only one (or possibly a few) action potentials will be elicited by the drug, because the adjacent membrane soon reaches a state of accommodation. This accommodation is indicated by the upward displacement of the broken line representing threshold. If the nerve is now stimulated (figure 10c at nn) an endplate potential is produced, but no action potential results because threshold cannot be reached.

The paradox of why decamethonium blocks "by depolarization" whereas acetylcholine stimulates can thus be resolved by recognizing that the prolonged depolarization by decamethonium raises the threshold so that the depolarization produced by the transmitter ends up below threshold.

ANTAGONISM OF COMPETITIVE BLOCK BY DECAMETHONIUM

This is not a practical phenomenon that might be of use in anesthesiology, but it is a pharmacologic interaction worth understand-

ing. Suppose decamethonium is added in the presence of a competitive block (figure 10d). Because tubocurarine is occluding receptors, the decamethonium will produce less depolarization than it did without tubocurarine in figure 10c. However, some depolarization results and produces a step upon which the small endplate potential produced by nerve stimulation (10d at nn) may reach threshold. (Members of the Watusi tribe in Africa can jump over seven feet. They do so, however, by placing a small mound of earth in front of the pole, and thereby give themselves a little extra head start. The decamethonium serves as such a pedestal for the endplate potential, enabling it to reach a threshold it might otherwise not attain).

ANTAGONISM OF DEPOLARIZATION BLOCK BY TUBOCURARINE

Again we are discussing an interaction of mainly academic interest. It is not practical to use this sort of antagonism in anesthesiology; the choice of dose is too critical. However, if tubocurarine is added to a muscle blocked by decamethonium, the tubocurarine will occlude a considerable fraction of the receptors so that the decamethonium will no longer be able to sustain a large depolarization. The membrane will repolarize (figure 10e) and the threshold will return towards normal (broken line). A situation will be reached which is equivalent to that in figure 10d just before the nerve was stimulated and nerve stimulation will produce the same effect as is 10d.

Phase II Block

All the discussion so far deals with the depolarization block seen when decamethonium is first added. This block, as should be clear by now, is consistent with known behavior of cell membranes. With time, the depolarization fades¹² and the muscle passes into a state where it is still blocked, but the mechanisms just described cannot be invoked to explain this later stage because there is no depolarization to lead to accommodation in the adjacent electrically-excitable membrane. Furthermore, a competitive mechanism seems unlikely because there is no reason to believe that the maximal occupancy by decamethonium

would not be reached immediately when the receptors are exposed to the drug.^{13, 14} There is no simple reason to expect a long-term increase in receptor occlusion. Phase II block therefore should not be called "competitive," even though agents which reverse tubocurarine block also reverse phase II block. There is more going on than simple competition. At present an explanation cannot be given.¹²

It is of interest, however, to suggest one possibility related to the above physiologic mechanisms. Normally, one assumes that the ionic concentration gradients are well maintained by the sodium pump and the fluxes associated with the action potential or the endplate potential do not appreciably disturb the concentrations on either side of the membrane. With decamethonium, however, there is a prolonged increase in permeability and considerable loss of potassium and influx of sodium probably occur. In fact, one can measure appreciable increases in plasma potassium after depolarizing agents.¹⁵ It may be, therefore, that with prolonged administration of decamethonium the cellular battery is run down. Phase II block would then be pictured as a situation in which the ions are distributed across the endplate membrane in such concentrations that they are at electrochemical equilibrium (*i.e.*, they are distributed passively) and the adjacent membrane pulls the membrane potential at the endplate back to somewhere near a normal resting value. The transmitter, when released, might then produce only a slight depolarization, so that although there is normally a considerable margin of safety in local action-current effects, and although accommodation would be absent in the adjacent electrically-excitable membrane, the neuromuscular junction would be blocked. Neostigmine might, by causing repetitive firing of the nerve terminal,¹⁶ now be able to tip the balance in favor of transmission.

This outlook is speculative and rather hard to test experimentally, but it is plausible and avoids postulating complicated and even more speculative and untestable changes in endplate receptors.

Summary

The mechanism of neuromuscular block by depolarizing agents such as decamethonium

seems quite compatible with our knowledge of behavior of excitable cell membranes.

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Color photo of a child by Edward K. Atkinson, M.D., Greenville, Pennsylvania, first prize winner in the color photo category at the 1967 Physicians' Art Exhibit at the 1967 Annual Meeting in Las Vegas.