Monographs in Anaesthesiology

Muscle Relaxants

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edited by Ronald L. Katz

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Edited by

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Preface

This book represents an attempt to provide the clinician with the basic material necessary for the rational use of muscle relaxants as well as the accumulated experience of clinicians with a basic science background. The experts chosen for this task were selected not only for their knowledge but more importantly for their ability to communicate this knowledge. The charge to the authors stated that since they were all acknowledged experts they did not have to prove this by writing obscure esorteric chapters. No prizes were to be given to the author with the most references or the earliest reference with the longest Latin title. The only prize would be the gratitude of the editor for the skillful blending of art and science.

When the chapters arrived certain decisions were made. In an attempt to keep the book from being equivalent to 300 mg of pentobarbital or having a MAC value of 3, the styles of the authors were not tampered with. Hopefully this will result in a change of pace which will stimulate the reader's reticular activating system. It was also realized that the same material was covered by several authors. Some of the duplication was retained in order to provide different ways of looking at the same thing or to demonstrate that the experts do not always agree or to allow each chapter to stand in its own right. In this regard I feel that the order of the chapters is only one of many possibilities. Other sequences, equally good or possibly better, were considered. Since each chapter is a complete unit the reader may select his own sequence. This book is dedicated

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Contents

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*Physiology and pharmacology of neuromuscular blocking agents**

B. E. WAUD and D. R. WAUD

Neuromuscular blocking agents find their principal clinical applications as adjuncts to anesthesia. Here they have two main uses. First, they can be used to prevent reflex laryngospasm during endotracheal intubation. Secondly, they can be used to reduce muscle tone, a low level of muscular contraction present as the result of a continuous unconscious efferent discharge through the motor nerves. At any given time only a small fraction of muscle fibers will actually be contracting, but this degree of activation is sufficient to produce appreciable tension in the muscle – enough to work against a surgeon trying to reduce a fracture, or to increase intra-abdominal pressure so as to expel viscera through an incision. It is possible to reduce the tonic nervous discharge by increasing the concentration of general anesthetic used. However, since this may have undesirable physiological consequences (like depression of myocardial competence) it is now customary to use the anesthetics to produce unconsciousness and introduce a second agent – one which blocks transmission of impulse from nerve to muscle – to relax voluntary muscles.

In order to understand the use of such neuromuscular blocking agents, one must first understand their mechanisms of action. These, in turn, can be meaningful only when the physiology of nerve, muscle and neuromuscular junction is understood. Therefore, the physiology relevant to the action of drugs at the

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neuromuscular junction will be discussed rather extensively so as to produce a unified picture.

The field of electrophysiology is dominated by the magnificent studies of Hodgkin and Huxley and of Katz. The last has summarized the area superbly in his book "Nerve, Muscle and Synapse" (1966). To make this present chapter more compact, we shall refer the reader to this monograph for most references to the original literature.

Muscular relaxation can result from interference with function at many points in the motor pathway. For purposes of the present description, a signal causing a muscle cell to contract can be pictured to follow the pathway:

central nervous system
↓
ventral root of spinal cord
↓
axon of somatic nerve (myelinated)
↓
nerve ending (unmyelinated)
↓
synaptic cleft
↓
motor end-plate
↓
muscle membrane
↓
excitation-contraction-coupling mechanism
↓
contractile mechanism

We shall be concerned with events at the motor end-plate. However, the electrophysiology of the region can better be understood if we begin with a consideration of the behavior of a nerve axon.

Nerve Conduction

In this section we shall try to present a framework in which one can view electrical behavior of a nerve axon in particular, and of excitable membranes in general. Before we turn to a detailed analysis of mechanism, it is useful to

describe some general features that can be demonstrated merely by recording potential changes in the region of the nerve.

The Membrane Potential. If a voltmeter is connected to a nerve trunk the cells are found to be equipotential along their length. If the nerve is crushed at one point, that area becomes negative *(injury potential)*. Apparently, the injury connects the electrode in the extracellular space to a negative cell interior, i.e. the resting cell membrane is polarized with the inside negative. Such a voltage difference is called a *membrane potential.* The membrane potential is the result of the presence of a semi-permeable membrane between solutions of different ionic concentrations. Why does a voltage difference occur? Suppose a membrane, permeable to potassium ions but not to chloride ions, separates two solutions of potassium chloride (Fig. 1). Because there is a concentration difference, both

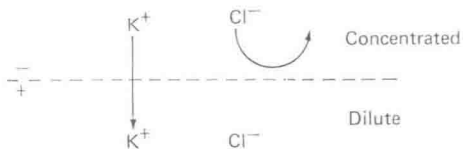

Fig. 1. A concentration cell. If solutions of potassium chloride at different concentrations are separated by a membrane permeable only to positive ions, the more concentrated solution will become negative as positive potassium ions diffuse across the membrane and leave negative chloride ions behind.

potassium and chloride ions will tend to move from the more concentrated to the more dilute solution. Only the potassium ions, however, are able to pass through the membrane; thus an excess of potassium ions (and positive charges) builds up on the side where the solution is more dilute. When the voltage difference caused by the increase in positive charge becomes large enough to be equal (and opposite) to the concentration gradient driving the potassium ions through the membrane, an electro-chemical equilibrium will be reached – with a potential difference across the membrane such that the side with the higher salt concentration is negative.

A more complicated model is shown in Fig. 2 where the ion concentrations are similar to those of a living cell. If the membrane were permeable only to potassium, the inside would become negative by the process described above. If the membrane were permeable only to sodium, the inside would become positive. We can then picture a scale for possible membrane potentials (Fig. 3). At one extreme (E_K) the inside will be about -100 mV, the value if the cell were behaving like a pure potassium battery. At the other extreme (E_{Na}) the inside will be about $+75$ mV, the value if the cell were behaving like a pure sodium

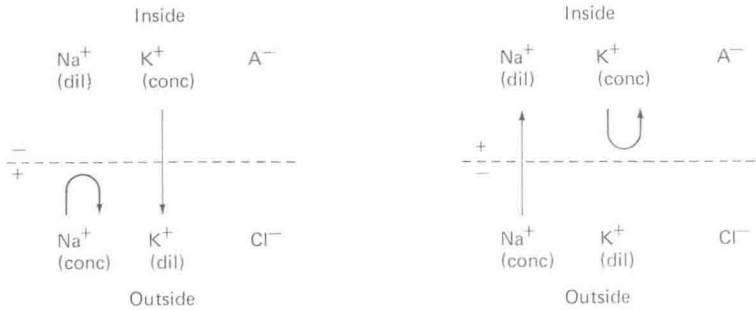

Fig. 2. A more complicated concentration cell. Concentrations correspond to those found inside and outside of excitable cells (A^- represents fixed negative changes inside the cell). If the membrane were permeable only to potassium ions (left panel), the inside would become negative. If the membrane were permeable only to sodium ions (right panel), the inside would become positive. If the membrane were permeable to both ions, the potential would fall between these extremes.

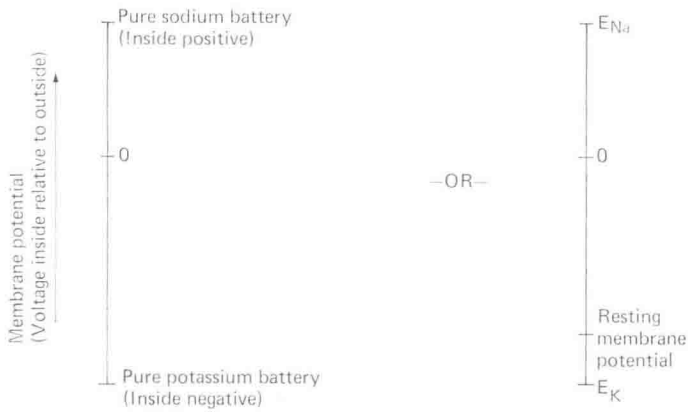

Fig. 3. Scale of possible cell membrane potentials. The bottom of the scale corresponds to the left-hand panel in Fig. 2, the top to the right-hand panel. Changes in relative permeabilities to sodium and potassium will shift the membrane potential up or down between these extremes.

battery. The scale shown in Fig. 3 forms the basis for analysis of the electrical behavior of biological membranes; the position the membrane takes on the scale is determined by the relative permeabilities to sodium and potassium.

The actual *resting membrane potential* found in nerve cells is about −90 mV, indicating that the cell behaves mainly like a potassium battery with a slight permeability to sodium.

The membrane is also permeable to chloride; however, chloride ions distribute themselves passively (so that E_{Cl} is near E_K). Therefore, the effect of chloride ions may be ignored without introducing too much inaccuracy.

Unlike a system with a perfectly semi-permeable membrane, the nerve cell does not reach a true equilibrium, but only a steady state which requires energy for maintenance. "Running down" is prevented by the sodium pump, which ejects sodium that leaks in, and maintains the potassium concentration gradient. The role of the sodium pump then is to keep the "battery" charged. As long as this job is done, the required concentration gradients will exist in the concentration cell and the sodium pump need not be considered explicitly in the analysis of voltage changes. All voltage changes in the cell will be the result of changes in membrane permeability. The membrane potential will lie somewhere on the scale of Fig. 3; the actual position will be governed by the relative permeabilities to potassium and sodium.

The Action Potential. How is a signal conducted along an axon? If we examine the distribution of an injury potential, we find that it does not spread very far. The situation is analogous to the passage of signals along a trans-Atlantic cable. In both cases the signal dies out with distance. Engineers counteract this effect in the cable by periodically introducing amplifiers to bring the signal back up to its original level. Nerves behave similarly; the axon membrane has an amplifying system to regenerate the signal along its path. Some properties of this system can be seen with a simple external recording system. As the nerve impulse passes under an electrode, that electrode becomes negative, i.e. activity is associated with a wave of negativity passing along the axons. This electrical change associated with the signal is called an *action potential.* It can be initiated by applying a brief pulse of current with a cathode, i.e. by causing current to flow outward from the axons. In any given axon, activation is found to be an all-or-none process. Up to some value of stimulus strength, a propagated action potential does not occur; above that strength *(threshold)*, a full action potential results. Stronger stimuli do not produce larger action potentials.

The above observations led neurophysiologists to conclude that during activity the selective permeability of the membrane was lost so that it was no longer polarized, i.e. the membrane potential fell to zero. However, when a large nerve preparation – the giant axon of the squid – became available, it was possible to record the internal potential directly. The resting membrane was negative inside as expected, but the action potential was found to be the result of more than a simple membrane breakdown – the potential *reversed* polarity, i.e. the inside of the cell became positive. This led to Hodgkin and Huxley's (1952) classic reanalysis of the nature of the action potential. We turn now to a description of their model of the action potential.

During an action potential, there are many factors that change with time: voltage, position of the activity along the axon, and membrane permeabilities

to sodium and potassium. To simplify the analysis, Hodgkin and Huxley kept all but two or three constant. Specifically, they threaded a wire down the center of a squid giant axon so that all the membrane was activated in synchrony (i.e. position of the active process along the axon was no longer a variable); they then connected electronic amplifiers so that the membrane potential could be kept constant ("voltage clamp") at a predetermined value (i.e. voltage was no longer a variable). Only sodium and potassium permeabilities were left to vary and the effect of the former could be eliminated by working in a sodium free medium. Thus, they were able to reduce a complicated system to an analysis of the time course of current carried by potassium plus sodium or by potassium alone (the sodium current then could be calculated by subtraction). The result of such experiments can be summarized by a diagram such as that in Fig. 4.

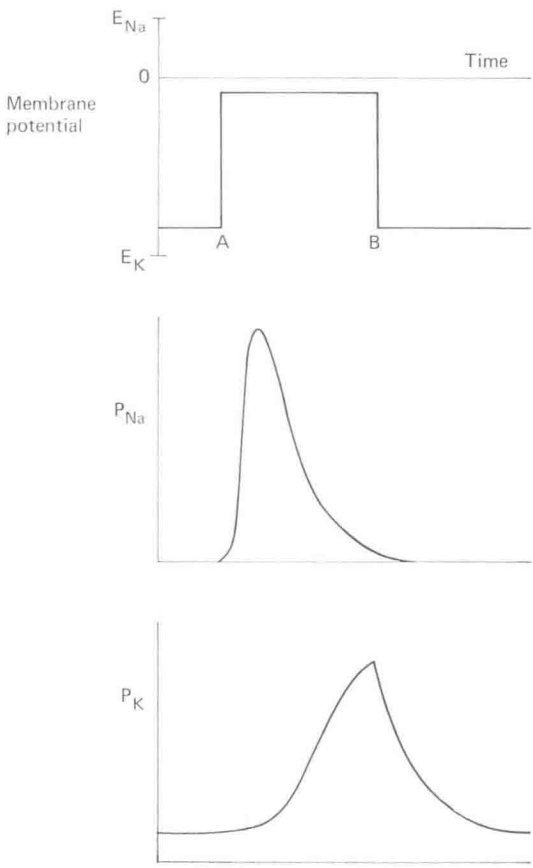

Fig. 4. Diagram of behavior of an electrically-excitable membrane. After Hodgkin and Huxley (1952).

In this diagram, ionic permeabilities to sodium and potassium (P_{Na} and P_K) are followed, rather than ionic currents, since it is a change in a membrane property – permeability – that allows the currents to flow – i.e. permeability changes are more fundamental. When the membrane is depolarized (at A), there is an increase in permeability to sodium and a delayed increase in permeability to potassium. Even though the membrane is held depolarized, the sodium mechanism turns off spontaneously. However, the potassium permeability remains elevated until the membrane is repolarized (at B). Repolarization also "reactivates" the sodium mechanism (i.e. returns it to a state where it can be turned on by a subsequent depolarization).

Fig. 5 shows how these two fundamental changes – (i) a transient increase in permeability to sodium and (ii) a delayed increase in permeability to potassium,

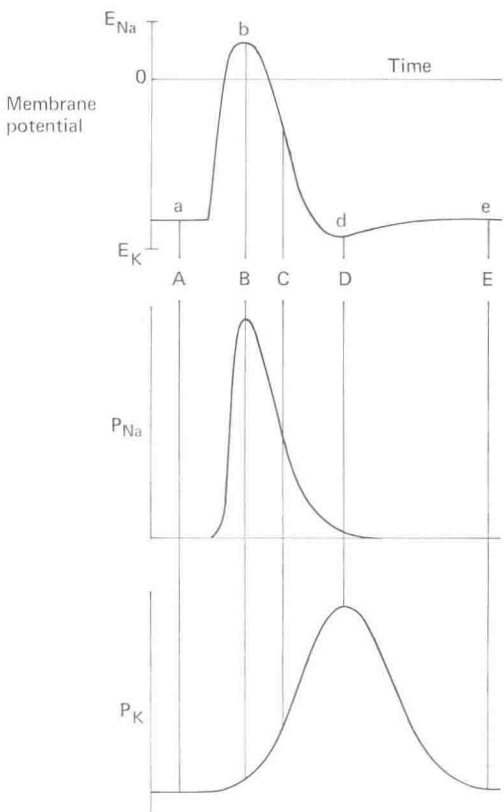

Fig. 5. Diagram to illustrate how specification of the behavior of the time course of sodium and potassium permeabilities provides an explanation of the shape of an action potentia (see text).

generate an action potential. Consider the five times indicated by the vertical lines A–E. In the resting state (A), $P_K \gg P_{Na}$, so the membrane potential lies near E_K at a. Now suppose the membrane is depolarized slightly; P_{Na} will rise and fall and P_K will do the same with a slight delay. Some sodium ions may rush into the cell to depolarize it somewhat further than the point reached by the initial stimulus – but if the initial stimulus was not too great, the whole process will die away and no action potential will result. If the stimulus is made larger and larger, a point will be reached *(threshold)* where the process no longer dies away but is amplified. Specifically, the depolarization increases P_{Na}, sodium ions rush in to depolarize the membrane still further so P_{Na} rises more and so forth until the sodium mechanism is turned on to its full extent. At this point (B), $P_{Na} \gg P_K$ (since the increase in P_K is delayed) so the membrane potential is shifted up to b near E_{Na}. Now the P_{Na} begins to fall and P_K begins to rise. As they approach each other, the membrane potential moves back to a value between E_{Na} and E_K (c). Later still, P_{Na} has fallen to its resting level while P_K is still higher than its resting level. At this point (D), the membrane potential is even more negative (d) than the resting potential. (For historical reasons this is called a *positive after potential* because it appeared as a wave of positivity when recorded extracellularly.) Finally at (E), P_K returns to its original level and the membrane to its resting potential (e).

Fig. 5 can be viewed not only as an illustration of how a specific phenomenon – the action potential – comes about, but also as a demonstration that consideration of changes in P_{Na} and P_K provides an appropriate framework in which to view electrical events. A knowledge of the behavior of P_{Na} and P_K was sufficient information to permit one to deduce the voltage changes that would result. This is why the scale in Fig. 3 is our basic frame of reference.

The electrical change associated with the passage of an impulse along the nerve is self-propagating. Movement of sodium ions to the inside of the cell produces a net flow of positive charges inward across the membrane. Since electrical charges cannot pile up at one point, this positive current flows axially along the core of the nerve cell and out through an adjacent part of the membrane to complete the circuit (Fig. 6, top). This outward passage through the membrane is exactly what is needed to repeat the process described above. The current loops are called *local action currents.*

The description of the nerve action potential so far has been that of an unmyelinated nerve (like the squid axon on which most work has been done). One more feature must be added to make the model applicable to myelinated nerve – the phenomenon of *saltatory conduction* (from the Latin saltare, to dance). The point is simply that most of a myelinated nerve is covered by a non-polar sheath which acts as an electrical insulator. Thus, it is only at the nodes of