The physiology and pathophysiology of the myoneural junction

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This article presents a concise review of the normal anatomy and physiology of neuromuscular transmission as well as the pathophysiology of some disease states. It also offers a brief review of the anesthetic management of some of these conditions.

This review explains the structure and function of the normal neuromuscular junction and its alteration by disease processes. Consideration will be given to the anatomy of the motor nerve as it approaches the muscle innervated, the microscopic anatomy of the nerve terminal, and the metabolic functions performed by this structure as well as the structure and function of the cholinergic receptor underlying the nerve terminal and extrajunctional muscle membrane. Some of the commonly encountered neuromuscular diseases are also discussed in relation to the anesthesia management.

The anatomy of neuromuscular transmission

Though many structures in the brain and spinal cord influence neuromuscular function, it is reasonable to begin our consideration of neuromuscular transmission with the concept of the motor unit. This consists of the motor neuron, its axon and terminal branches as well as the muscle cells innervated.

The axon acquires a myelin sheath as it exits the anterior horn cell through the axon hillock. The axon maintains this myelin sheath until it is within 100-200 microns of the muscle cells which the axon is destined to innervate. At this point the axon loses its myelin sheath and divides into a number of terminal branches. Each of these branches will supply a single muscle cell (Figure 1). The number of muscle cells per motor unit varies with the function of the muscle innervated. Muscles which perform finer movements, such as the intrinsic muscles of the hand or the extraocular muscles, have relatively few cells per motor unit while those muscles involved in gross movements, such as those of the hip, would have a larger number of muscle cells per motor unit. The motor axon branches terminate in specialized structures called motor nerve terminals. The motor nerve terminal lies in a groove on the surface of the muscle known as the synaptic gutter and is covered by a Schwann cell. The motor nerve terminal functionally lies in the intercellular space. Light and transmission electron microscopy reveal that the motor nerve terminal contains mitochondria which are necessary for the metabolic functions of the nerve terminal. It also contains round bodies called synaptic vesicles, which contain acetylcholine molecules.

It should be remembered that this motor nerve terminal may be a meter or more distant from the cell body. Perhaps it is because of this that the motor nerve terminal has been designed in such a manner so as to be able to carry out
many metabolic processes on its own. In addition, the phenomena of both slow and fast axonal transport bring metabolic products and substrates from the cell body to the periphery. This is well demonstrated in the ability of drugs which block axonal transport to cause profound changes in neuromuscular transmission.

Though both light and transmission electron microscopy have revealed much information regarding the structure of the motor nerve terminal, they have provided little information concerning the structure of the nerve terminal membrane. In rare instances, transmission electron microscopy has revealed what appears to be a synaptic vesicle opening into the subsynaptic cleft, but other information concerning transmitter release has yet to be obtained. The advent of scanning electron microscopy and the use of freeze-fracture techniques have made it possible to identify bars on the nerve terminal membrane. These are associated with what appear to be synaptic vesicles, which look as if they are about to be extruded into the synaptic cleft. The bars have been interpreted as being active sites for release of acetylcholine.

The synaptic cleft is the area underlying the nerve terminal, separating it from the post-synaptic membrane and the muscle beneath (Figure 2). The cleft is about 150 Ångstrom units (10^{-8} m) wide. There is some debate as to whether the synaptic cleft is filled with a specialized fluid or a simple aqueous ionic solution comparable to extracellular fluid. Some staining techniques give evidence that the synaptic cleft contains a variety of hydrated basement membrane material. What has been well demonstrated, however, is that there is no direct membrane-to-membrane contact between the nerve terminal and the underlying muscle membrane.

The muscle cell membrane underlying the nerve terminal differs from the rest of the muscle membrane, being composed of folds and valleys and having been functionally modified to serve as the cholinergic receptor. The gap directly underlying the nerve terminal is known as the primary synaptic cleft and the invaginations of this gap into the muscle are known as the secondary synaptic clefts.

With most types of microscopy, except for the presence of these folds, the muscle membrane appears to be quite uniform. Freeze-fracture techniques, however, have demonstrated a peculiar granularity of this part of the membrane. This granularity, which has a definable regular structure, has been interpreted as being the cholinergic receptor.

**Physiology of neuromuscular transmission**

To understand the physiology of neuromuscular transmission, one must have some knowledge of the structure and function of the cell membrane since the neurotransmitter released from the nerve terminal must cross the cell membrane into the synaptic cleft in order to activate the underlying muscle cell and generate an action potential.

The structure of the cell membrane as it is currently understood is based on the initial description by Davson and Danielli (Figure 3). These investigators hypothesized a cell membrane com-

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**Figure 1**

Diagram of a motor unit. Note that the axon loses its myelin sheath before dividing into its terminal branches and the axon innervates more than one cell. Encircled area is amplified in Figure 2.
posed of a phospholipid bilayer so arranged that the lipid moiety of each half layer forms the central part of the membrane and the surface of the membrane, which is composed of phosphate heads. Thus, the center of the membrane is formed by the hydrophobic lipid groups and the external surfaces are composed of hydrophilic phosphate heads.

It has also been suggested that a protein layer covers both surfaces of the cell membrane or that there are large globules of protein which partially or completely penetrate the thickness of the membrane. Those protein globules which completely penetrate the membrane may be the channels through which ions flow into and out of the cell. Although these channels have not been structurally identified, the validity of their existence has been supported by physiologic studies.\(^7\)\(^8\)

The cell membrane is differentially permeable to various ions (Figure 4). However, this selectivity is more complex than might initially be appreciated. If one assumes that a common channel is used by both sodium and potassium, then the ion having the smaller radius should transfer across this channel more easily. This would suggest that sodium, having the smaller ionic radius, should pass through the membrane easier than potassium which has a larger ionic radius. Since this is not the case, most investigators consider that the hydrated ionic radius may be more important than the unhydrated ionic radius.

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**Figure 2**
A neuromuscular junction. Note the presence of acetylcholinesterase and cholinergic receptor on the nerve terminal and postsynaptic membrane.

**Figure 3**
Schematic representation of a cell membrane. The pores or channels are the pathways for ionic fluxes. The "Ca++" signifies that it may be part of the gating mechanism.
Under these circumstances potassium, with the smaller hydrated ionic radius, would therefore pass more easily than sodium through the channel. This transfer of ions across the membrane based on the hydrated radius more nearly agrees with the investigative evidence. Membrane permeability to other ions also exists and there is good evidence that both calcium and chloride ions cross the membrane. However, for a basic understanding of the principles involved in the maintenance of membrane potential and the generation of the action potential, only the permeability of sodium and potassium ions need be considered.

In addition to this passive transport, there is also an active transport system for moving sodium ions out of the cell and moving potassium into the cell against ionic concentration gradients. This mechanism is called the sodium pump. The sodium pump functionally resembles a sodium-potassium activated adenosinetriphosphatase (ATPase). This sodium and potassium activated ATPase, when it faces the internal environment of the cell, appears to have a high specificity for sodium to which it will attach. It transports the sodium ion to the external surface of the cell where it is then released.

The pump, now on the external surface of the cell, changes its specificity so that it now attaches to potassium ions and transports them back into the cell. Thus, the sodium potassium pump mechanism tends to keep the intracellular content of sodium low while augmenting, to a relatively small extent, the intracellular content of potassium. The principal function of this pump appears to be transporting out of the cell the sodium which had entered during the action potential.

There is an electric potential difference of $-70$ to $-90$ mv across the cell membrane. This potential can be measured using glass microelectrodes. Thus, measured in the resting cell, it is called the resting membrane potential and is caused by the differential permeability of the membrane with respect to sodium and potassium ions. Having the smaller hydrated ionic radius and a high ionic gradient, potassium diffuses out of the cell and leaves behind large amounts of chloride and other anions, giving rise to the negative intracellular potential.

This negative intracellular potential is ordinarily counteracted to only a small extent by the limited influx of sodium into the cell. Even though the ionic gradient for sodium is rather high, its influx is limited by its low permeability. The amount of sodium within the cell is also limited by the activity of sodium pump.

One of the prime properties of the cell membrane of excitable tissues is the ability to generate an action potential in response to a proper stimulus. This stimulus may be either electrical, chemical or mechanical depending on the tissue involved. As a general rule, tissues that are electrically excitable are chemically inexcitable and vice versa. In neuromuscular transmission, this has considerable significance in that the extrajunctional membrane is not sensitive to chemical stimuli while the post-junctional membrane underlying the nerve terminal and containing the cholinergic receptor is relatively insensitive to electrical stimulation.

Each excitable tissue cell possesses a critical threshold for action potential generation. This critical potential is known as the threshold. At the post-synaptic membrane, this depolarization to the threshold value is called the endplate potential (EPP) (Figure 5). When the cell membrane is rapidly depolarized to this threshold value, sodium channels within the membrane open, permitting the rapid influx of sodium ions. This rapid influx of sodium leads to further depolarization which
usually surpasses 0 potential by 10-30 mv. The rapid rising phase of the action potential is known as the spike and the extent beyond zero to which it rises is known as the overshoot.

Even while the membrane is still depolarizing, a process begins in the membrane to terminate the action potential. This process consists of the closing of the sodium channels and is known as sodium inactivation. Beginning somewhat later than the sodium influx is a potassium efflux which is of lower magnitude and longer duration and results in repolarization of the cell membrane toward its normal resting value.

The cell membrane does not immediately return to this value but oscillates above and below it for a few milliseconds until it finally stabilizes at its resting level. These oscillations are known as negative or positive after potentials depending on whether they are above or below the resting value of the membrane potential.

The physiologic mechanisms underlying the opening and closing of the ionic channels responsible for action potential generation and the repolarization of the cell membrane are not completely understood. Good evidence exists indicating that they are subject to a gate-like mechanism. Some studies suggest that, in many cell membranes, this is a function of calcium ions. There is evidence to suggest that the mode of action by which local anesthetics function as membrane stabilizers may be related to their interaction with calcium. Others, however, do not agree with this suggestion and feel that the site of action of calcium as a gate-like mechanism and the mode of action of local anesthetics as membrane stabilizers are separate.

**Neuromuscular transmitter**

Acetylcholine (ACh) is now accepted as being the transmitter at the neuromuscular junction (Figure 6) as well as for all pre-ganglionic autonomic transmission and post-ganglionic parasympathetic transmission.

The synthesis of acetylcholine begins with the two carbon acetate groups derived from glucose metabolism. This two-carbon group is coupled
with co-enzyme A to form acetylcholine-co-enzyme A or *active acetate*. The source of choline, an amino alcohol, is primarily dietary. Acetyl-coenzyme A combines with choline in the presence of the enzyme cholinacetylase to form acetylcholine.

Storage of acetylcholine occurs in two forms. A readily available store is responsible for the spontaneous release which occurs constantly at the nerve terminal and gives rise to miniature end plate potentials. This immediately available store also provides the acetylcholine which gives rise to the first few end plate potentials of a tetanic train. The other mode of storage is a remote store, which appears to be the larger of the two and has a primary function of replenishing the readily available store during stimulated release.

Following its release from the nerve terminal and its activation of the cholinergic receptor, acetylcholine is hydrolyzed very rapidly by an enzyme, acetylcholinesterase, located on both the muscle cell and nerve terminal. The breakdown products of the acetylcholine are acetate and choline. The acetate is taken up by the blood and enters the common metabolic pool while choline (like catecholamines at the adrenergic nerve terminal) is subject to reuptake by the motor nerve terminal for further synthesis of acetylcholine.

The acetylcholinesterase responsible for hydrolysis of almost all the acetylcholine at the neuromuscular junction is a membrane bound enzyme of high substrate specificity. It has two binding sites referred to as *anionic* and *esteratic*. The anionic site is responsible for the high substrate specificity, while the esteratic site, showing high affinity for other esters, is of low specificity.

There is another cholinesterase in the plasma (plasma cholinesterase or pseudocholinesterase) which has a lower substrate specificity and will hydrolyze, at a lower rate, the acetylcholine that

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**Figure 6**

Acetylcholine cycle. Choline is subject to re-uptake to the nerve terminal analagous to catecholamine in the adrenergic system.

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leaks away from the neuromuscular junction. It also hydrolyzes many other ester compounds including procaine, tetracaine, and succinylcholine.\textsuperscript{13}

Our knowledge of the physiology of the nerve terminal is based primarily on interpretation of post-synaptic recordings. When a microelectrode is inserted into the end plate region of a muscle cell, small deflections of about 0.5 mv in amplitude, known as \textit{miniature endplate potentials} (MEPPS) can be recorded. These are due to the random release of individual packets, or quanta, of acetylcholine at the nerve terminal. This spontaneous release goes on constantly.

In addition to this spontaneous release, acetylcholine is subject to stimulated release. The advent of a nerve action potential into the nerve terminal causes the release of a few hundred quanta of acetylcholine almost simultaneously. When the EPP caused by this acetylcholine release reaches a critical amplitude or threshold of the muscle cell, a muscle action potential results.\textsuperscript{14}

There is some disagreement among investigators concerning the amplitude of the EPP. Albuquerque\textsuperscript{15} believes that there is little or no difference between EPP amplitude and threshold for action potential generation in the muscle, and hence a narrow margin of safety. Others believe that there is a wide margin of safety in neuromuscular transmission.\textsuperscript{16, 17, 18} They estimate EPP amplitude to be about four times higher than the muscle membrane threshold.

As previously stated, the immediately available store is most likely the source of acetylcholine for spontaneous release and for the first few action potentials of the tetanic train. A prolonged tetanic stimulation causes mobilization of acetylcholine from the remotely available into the immediately available store. This process can be seen when evaluating EPP amplitudes during a tetanic train.

The first endplate potential will be the highest and the amplitude of each succeeding EPP will decrease until a plateau level is reached. This progressive decrease of EPP amplitude during the initial phase of a tetanic train of stimuli is known as \textit{early tetanic rundown}.\textsuperscript{19} The maintenance of this plateau amplitude is a function of the rate of mobilization of acetylcholine from the remote store.

Evidence of the presence of cholinergic receptors on the post-synaptic membrane can be documented by recording membrane potential changes with application of acetylcholine to the junctional area. Recent use of radioactive labeled \textit{a}-bungarotoxin has made it possible to quantitate, with some degree of certainty, the number of receptors on the muscle membrane.\textsuperscript{20} This toxin can also be coupled with an electron dense ligand and its presence noted with electron microscopy. This staining procedure has demonstrated the cholinergic receptor not only post-synaptically but also pre-synaptically on the nerve terminal. The function of this pre-synaptic cholinergic receptor has not been completely elucidated.

Calcium has multiple functions in neuromuscular transmission and muscle function. This ion, as previously mentioned, serves as a membrane stabilizer and functions in the gate-like mechanism for ionic fluxes across the cell membrane. Calcium performs this function both pre-synaptically and post-synaptically. In addition, the calcium ion plays an integral part in the formation of acetylcholine release sites on the nerve terminal.\textsuperscript{21} Calcium also has an important role in facilitating the coupling of the contractile proteins (actin and myosin) in the muscle, thus producing a shortening of the muscle fibers.

The action of calcium at these various sites is somewhat antagonistic. Although an increase in calcium ion facilitates transmitter release and enhances muscle contraction, it also has a stabilizing effect on the cell membrane. Conversely, lowered concentrations of calcium which would destabilize the membrane also would have an inhibitory effect on transmitter release and muscle contraction.

The final effect of calcium concentration in any given clinical circumstance cannot, at this time, be stated with any degree of certainty. It has been our experience, however, that the lowering of ionized calcium by hyperventilation to a point which will produce tetany still results in indirectly elicited contraction.

\textbf{Pathophysiologic states}

A wide variety of musculoskeletal diseases involve pathology of the myoneural junction. Consequently, a characteristic of these conditions is abnormal neuromuscular transmission. Some of these disease states are greatly affected by the administration of anesthesia while others tolerate anesthesia well. Among the disease states involving the pathology of the neuromuscular system are myasthenia gravis, myasthenic syndrome, myotonia congenita, myotonia dystrophica, paramyotonia, malignant hyperthermia, severe burns, multiple trauma and spinal cord injury.

\textit{Myasthenia gravis and myasthenic syndrome.} The pathology of myasthenia gravis involves decreased sensitivity of the post-synaptic membrane.
to acetylcholine. This appears to be the result of a decrease in the number of cholinergic receptors. The amount of acetylcholine released from the nerve terminal appears to be normal. The pathology may involve an auto-immune process.

The diagnosis is based on: 1) the history of easy fatigability; 2) demonstration of fatigue with tetanic stimulation followed by post-tetanic facilitation and post-tetanic exhaustion on electromyography (EMG); and 3) subjective and objective improvement with edrophonium.

Preoperative preparation requires adequate control of myasthenic symptoms, by medication or plasmapheresis, optimum electrolyte concentrations and absence of respiratory infections. Minimal medication should be used to avoid respiratory depression. No single anesthetic agent appears superior, though local or regional anesthetic techniques are preferable where feasible. Muscle relaxants are seldom needed. If they are needed, however, small doses of nondepolarizing agents are preferred because of their predictability and reversibility.

Postoperative respiratory support is usually needed for 2-3 days after thoracotomy, sternotomy or upper abdominal procedure. The need for postoperative respiratory support can be predicted.

The myasthenic syndrome seen in patients with oat cell carcinoma of the lung is characterized by proximal limb muscle weakness. The EMG differs from that of myasthenia gravis in that the amplitude decreases with single stimuli and increases with repeated tetanic stimulation. Post-tetanic facilitation is present but not post-tetanic exhaustion. There is increased sensitivity to both depolarizing and nondepolarizing relaxants. The perioperative problems of the patient with myasthenic syndrome are similar to those of myasthenia gravis but usually less severe.

Myotonia dystrophica is a multisystem, inherited disease. The pathophysiology appears to be a degenerative process involving both motor nerve and muscle, producing changes which resemble denervation. This is manifested as a contracture of the skeletal muscle in response to cholinergic agonists and succinylcholine. Cardiac involvement, in the form of conduction defects as well as respiratory abnormalities, are seen in almost all patients.

Diagnosis is based on family history, the observation of dystrophic changes in muscle and the demonstration of myotonia. In EMG recordings, the myotonia is expressed as continuous low voltage activity, with higher voltage, fibrillation-like potential bursts. Mechanical stimulation of the muscle evokes a classic "dive bomber" effect; a rhythmical activity initially at 90-100 Hz which slows over a few seconds to a low voltage, slow activity.

It is important in the preoperative evaluation to pay particular attention to assessment of both cardiac and respiratory function. These patients are particularly sensitive to barbiturates and manifest severe respiratory depression with very small doses. Except for a drying agent, preoperative medication should be omitted. The prevalence of cardiac irregularities requires close monitoring of cardiac function during anesthesia.

No single inhalation anesthetic agent is superior. Succinylcholine should be avoided because of the potential development of generalized myotonia. Local and regional anesthesia are preferred when applicable. Localized myotonia is best controlled by local anesthetic infiltration of the affected muscle. Systemic administration of nondepolarizing muscle relaxants are unlikely to relieve localized myotonia. However, Baraka has reported relief of succinylcholine-induced generalized myotonia by a large dose of d-Tubocurarine.

Burns, multiple trauma and neurologic injury. These entities, though apparently quite different, have in common a pronounced rise in serum potassium levels occurring after the administration of depolarizing relaxants. The underlying pathology in all of these cases is most likely cholinergic receptor spread to involve large areas of the muscle membrane. This results in an increased potassium efflux from the muscle compared to the normal on exposure to a cholinergic agonist.

Why skeletal muscle has this response to such a wide variety of injuries is not understood. Specifically, in spinal cord transection, there appears to be a 2-3 day period between the injury and the development of hyperkalemia. On theoretical grounds, the same problem should exist in patients with demyelinating disease.

The presence of muscle disease does not always carry a high risk during anesthesia. Some conditions which tolerate anesthesia fairly well are myotonia congenita, paramyotonia, the muscular dystrophies and familial periodic paralysis.

REFERENCES


AUTHORS

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