CHAPTER 13

Myasthenia Gravis and Myasthenic Syndromes

Mark B. Bromberg

The neuromuscular junction (NMJ) has a complex anatomy and physiology but usually functions with extraordinary reliability. The uniqueness of the NMJ becomes apparent in the expression of clinical disease that results when junctional transmission fails.

This chapter reviews the normal and clinically relevant anatomy and physiology of the NMJ followed by essential features of the clinical and laboratory diagnosis, pathology, therapy, and prognosis of the NMJ disorders, especially myasthenia gravis (MG). The chapter then considers the major NMJ disorders. There are many excellent reviews of MG in the recent literature (1).

THE MOTOR UNIT

The motor unit consists of a motor neuron, its peripheral axon process, and the muscle fibers it innervates (Fig. 1). The motor axon ends in an arborization of terminal branches, which each make synaptic contact with a muscle fiber at the NMJ. The number of muscle fibers innervated by a single motor axon varies from 20 to 1,500 (2). With rare exception, each muscle fiber is innervated by a single motor axon terminal branch (3). However, a small percentage of extraocular muscle fibers are multiply innervated (4). The NMJ is located midway along the length of an individual fiber, in the region called the motor point (3).

In disorders of NMJ transmission, the associated weakness results from failure of muscle fiber activation. Symptoms can at times be highly regional among muscle groups, within a muscle, and within motor units. For example, NMJs from neighboring muscle fibers may show stable transmission, variable transmission, or complete block of transmission (5).

M.B. Bromberg: Department of Neurology, University of Utah School of Medicine, Salt Lake City, Utah 84132.

FIG. 1. Schematic diagram of the motor unit and neuromuscular junction. Only a single terminal branch of the motor unit is shown. (From Ref. 7, with permission.)
NEUROMUSCULAR JUNCTION ANATOMY

Presynaptic

Terminal branches of the motor axon end over a region of the muscle fiber called the end-plate (Fig. 1). The end-plate is a specialized segment of muscle fiber membrane with a high concentration of junctional acetylcholine (ACh) receptors. There are also extra-junction ACh receptors distributed along the membrane in low numbers that do not have a role in normal NMJ function. The terminal axon branches remain covered by Schwann cells until they lose their myelin covering. At the end-plate region, the axon expands into a complicated array with varicosities called synaptic boutons (Fig. 1). These are complex entities with many organelles, including mitochondria and enzymes for synthesis and release of ACh. The synaptic vesicles contain ACh and specialized areas of the presynaptic membrane called active zones that contain calcium channels, where vesicular release occurs.

ACh is synthesized from acetyl-CoA and choline by the enzyme choline acetyl transferase. Fifty percent of the choline in ACh is recycled by an active presynaptic reuptake mechanism (6). After synthesis, ACh is sequestered within membrane-bound vesicles. Each vesicle contains about 5,000 molecules of ACh. There are a tremendously large number of synaptic vesicles in each bouton. Boutons cluster in rows along specialized regions of the presynaptic membrane that facilitate the secretion of ACh, called active zones, where vesicles fuse and ACh is released by exocytosis (7). Exocytosis is a complex process that depends on the influx of calcium into the presynaptic terminal (Fig. 2). The active zone also includes rows of large particles thought to be the calcium channels. To prevent an increase in presynaptic mem-
brane area by fusion of the membrane-bound vesicles, there is a recycling of excess membrane.

Postsynaptic

The presynaptic and postsynaptic membranes are separated by a gap of about 20 nm. The postsynaptic membrane is also highly specialized (8) and is thrown into deep folds that lie below presynaptic active zones (Fig. 1). The shoulders of the folds contain approximately 10,000 ACh receptors/μm², and voltage-sensitive sodium channels are situated beneath them. Clusters of molecules of acetylcholinesterase (AChE) are located in the depths of the folds. The primary mechanism of ACh inactivation is via the rapid hydrolysis of ACh into choline and acetate by AChE. Diffusion of ACh away from receptor sites is a lessener mechanism. The choline is actively taken up by the presynaptic membrane.

ACh receptors are pentameric protein complexes consisting of α, β, γ, and δ subunits (Fig. 3). The receptor complex spans the postsynaptic membrane, and the subunits form a pore which is the ion channel of the action potential (AP) along the muscle fiber (9). There is a constriction in the pore that opens when ACh binds to the external portions of the α subunits, allowing sodium, potassium, or chloride to pass. The density of ACh receptors falls off away from the end-plate region. Between the end-plate and the muscle fiber membrane, there is a perijunctional region that contains a mixture of ACh receptors and sodium channels where the muscle fiber action potential (AP) is initiated. The muscle fiber membrane contains voltage-dependent sodium channels that participate in the propagation of the AP along the muscle fiber (7). ACh receptors are nonstatic protein structures that are degraded and renewed in about 12 days.

![FIG. 2. Schematic diagram of the role of calcium on the release and mobilization of synaptic vesicles in the presynaptic terminal. A: Vesicles from the immediately available pool are docked at the active zone. Calcium channels are closed. B: The nerve action potential opens voltage-sensitive channels and the calcium influx facilitates vesicular release and mobilization of bound vesicles. (From Ref. 7, with permission.)](image-url)
NEUROMUSCULAR JUNCTION PHYSIOLOGY

Presynaptic

Voltage-gated calcium channels along the presynaptic membrane in the vicinity of the active zone initiate the process of NMJ transmission that begins with a motor nerve fiber AP (Fig. 2). Graded degrees of terminal depolarization result in graded influxes of calcium into the presynaptic terminal. The release of ACh, in turn, is dependent on and proportional to the concentration of calcium in the terminal. The release of ACh is not smoothly graded but occurs in quantal units. These are the number of ACh molecules contained in a single vesicle. The postsynaptic response includes the number of vesicles released and the nature of the interaction of ACh with the receptors. The number of vesicles released with each motor fiber AP, in turn, is related to the probability of release. The role of calcium in the presynaptic terminal is to enhance the probability of ACh release, and the magnitude of release is exponential with the concentration of calcium (9). The spontaneous release of vesicles produces a very small postsynaptic potential called the miniature end-plate potential (MEPP), which can be recorded during routine needle electromyography (EMG) studies as end-plate noise when the electrode tip is in the vicinity of NMJs at the motor point.

Calcium is required for the fusion of vesicles to the presynaptic membrane at the active zone and contributes to the dilation of the fusion pore between the vesicle and membrane, allowing release of ACh into the synaptic cleft (Fig. 2). Calcium is also involved in the mobilization of vesicles. The availability of vesicles for release of ACh can be considered to be distributed among several pools of ACh discussed later. In essence there is an immediately available pool, comprised of vesicles in the active zone; others are bound to the cytoskeleton. The influx of calcium frees the vesicles from a binding protein, making them available to move to the active zone for subsequent fusion and release of ACh (7). AChE is a molecule that floats above the end-plate membrane similar to a tethered balloon. There is competition between the ACh receptor and the AChase enzyme, and the initial high concentration of ACh favors the receptor. As molecules of ACh diffuse from the receptor, the enzyme hydrolyzes them into the precursors choline and acetic acid (6). Approximately 50% of the choline is taken up by the presynaptic membrane.

During a motor nerve AP, the concentration of calcium can rise a thousandfold within several hundred microseconds at the active zone where the calcium channels are most dense. The calcium buffering systems in presynaptic terminals are limited, and the repeated influx of calcium follows a train of high-frequency APs that saturates the system, leading to a residual calcium buildup. This increases the probability of vesicular release when the next nerve AP arrives. The buildup of calcium underlies the phenomena of posttetanic potentiation. The antagonism of calcium channels by high serum magnesium concentration blocks calcium-dependent release of ACh (7).

Postsynaptic

The α subunits are the sites where ACh attaches to open the receptor channel. One ACh molecule binds to each of the two subunits to bring about a conformational change in the receptor that increases the diameter of the pore or channel (Fig. 3). The concentration gradients of sodium, potassium, and chloride are such that sodium is the predominant ion flowing into the muscle fiber at the end-plate region. Normally, there is a rapid release of ACh from the presynaptic terminal that results in a near synchronous opening of approximately 20,000 receptor channels. The resultant end-plate current causes an EPP that depolarized the end-plate membrane (Fig. 4). The ACh concentration in the synaptic cleft falls rapidly due to hydrolysis by AChE and diffusion, and within a millisecond the channels close, causing a fall off of end-plate current flow. The EPP decays more slowly due to passive membrane properties of the muscle (7,9).

Under normal conditions the rising phase of the EPP reaches threshold, upon which voltage-dependent sodium
channels open and a muscle fiber AP is initiated (Fig. 4). The AP is propagated along the muscle fiber membrane to the ends of the fiber, leading to muscle fiber shortening and the development of force via excitation–contraction coupling.

Muscle fiber APs are clinically and electrodiagnostically important for two reasons. First, they are prerequisites for the development of force and shortening in a muscle. Second, electrodiagnostic studies record the extracellular AP as the compound muscle action potential (CMAP) during nerve conduction studies or as the motor unit action potential during needle EMG. Routine electrodiagnostic testing detects abnormalities of the NMJ only if there is a failure to initiate the muscle fiber AP. Single-fiber EMG (SFEMG) detects less severe abnormalities of the NMJ. A number of factors govern end-plate current flow and the shape of the EPP that are important in diseases of the NMJ. The rising phase of the EPP depends on the nearly simultaneous opening of a large number of channels in the AChR. In turn, the probability that a pore opens is largely determined by the concentration of ACh and the number of ACh receptors. Consequently, the rise time and amplitude of the EPP depend on the probability of release of ACh and the total number of receptors available.

**General Considerations**

Normally, the NMJ functions with complete reliability, transforming each motor nerve AP into muscle fiber APs in all muscle fibers of the motor unit. There are various mechanisms within the complexity of the NMJ, collectively called the “safety factor,” that ensure reliable NMJ transmission (10). These include an overabundance of ACh in the presynaptic terminals and more than adequate numbers of postsynaptic receptors. There is an immediately releasable pool of ACh in vesicles along the active zone (Fig. 2). There is another pool of vesicles bound to the cytoskeleton that are freed by calcium and that can be mobilized to the active zone for release. If the reuptake of choline is blocked experimentally by hemicholinium and the NMJ is activated to functional depletion of ACh, approximately 20% of the total ACh store still remains, presumably in a pool unavailable for release. The number

---

**TABLE 1. Descriptive model of the dynamics of normal NMJ transmission during low-frequency repetitive nerve stimulation**

<table>
<thead>
<tr>
<th>Stimulus number</th>
<th>ACh pool</th>
<th>Available ACh quanta</th>
<th>ACh quanta released</th>
<th>Resultant EPP amplitude (mV)</th>
<th>Action potential threshold reached</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Immediate</td>
<td>1,000</td>
<td>200</td>
<td>60</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Immediate</td>
<td>800</td>
<td>160</td>
<td>48</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Immediate</td>
<td>640</td>
<td>128</td>
<td>38</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Mobilizable</td>
<td>&gt;640</td>
<td>&gt;128</td>
<td>&gt;38</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Mobilizable</td>
<td>&gt;640</td>
<td>&gt;128</td>
<td>&gt;38</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Two ACh pools (immediately available and mobilizable) are under the influence of the influx of calcium into the presynaptic terminal. Mobilization of ACh ensures the release of an adequate number of ACh quanta. Because there are normal numbers of ACh receptors, each EPP exceeds the threshold for generating an action potential.

*In this model, the EPP amplitude must be greater than 30 mV to reach threshold for generation of a muscle fiber action potential.*

NMJ, neuromuscular junction; ACh, acetylcholine; EPP, end plate potential.

Modified from Albers JW, AAEM Workshop on Repetitive Stimulation.