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Diseases of Chemical Transmission at the Nerve-Muscle Synapse: Myasthenia Gravis

Myasthenia Gravis Affects Transmission at the Nerve-Muscle Synapse
   Physiological Studies Showed a Disorder of Neuromuscular Transmission
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Identification of Antibodies to the Acetylcholine Receptor
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Immunological Changes Cause the Physiological Abnormality
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An Overall View

In the preceding chapters we examined the mechanisms by which chemical transmitters are synthesized and released by neurons and the functional consequences of activating neurotransmitter receptors. Chemical transmission between neurons and their target cells is disrupted by many diseases. By analyzing such abnormalities in transmission, researchers have shed light on the mechanisms underlying normal synaptic function. The most common and most thoroughly studied disease affecting transmission is myasthenia gravis, a disorder of function at the synapse between cholinergic motor neurons and skeletal muscle.

There are two major forms of myasthenia gravis (the term means severe weakness of muscle). The most prevalent by far, and the only one known until about two decades ago, is the autoimmune form. Myasthenia gravis is the prototypical human autoimmune disease; fulfilling all the criteria proposed by Daniel Drachman: (1) An antibody is present in almost all cases. (2) The antibody reacts with an antigen that is important in the pathophysiology of the disease. (3) Features of the disease can be reproduced by transferring the antibodies to experimental animals. (4) An experimental form of the illness can be induced by immunizing animals with the antigen. (5) Therapeutic reduction of antibody levels ameliorates symptoms. The prevalence of autoimmune myasthenia is estimated to be 50–125 patients per million population, or about 25,000 affected people in the United States at any time.

The second form of myasthenia is congenital and heritable; it is not autoimmune and is heterogeneous. Fewer than 100 cases have been identified, but analysis of the congenital syndromes has provided information about the organization and function of the human neuromuscular junction. We will discuss this form later in the chapter.

In autoimmune myasthenia gravis, antibodies are produced against the nicotinic acetylcholine (ACh) receptor in muscle. These antibodies interfere with synaptic transmission by reducing the number of functional receptors or by impeding the interaction of ACh with its receptors. As a result, the skeletal muscle becomes weakened. This weakness has four special characteristics:
stimulation of the nerve produces a decremental response of the evoked motor action potential. Moreover, when the eyelids are affected, gazing upward for long periods aggravates the ptosis. However, an emphasis on symptomatic fatigue can be misleading. For one thing, weak muscles, regardless of the cause, are likely to fatigue more rapidly than normal. And patients with myasthenia generally complain of weakness, not fatigue in the sense of tiredness or lack of energy.

**Myasthenia Gravis Affects Transmission at the Nerve-Muscle Synapse**

The first well-documented example of myasthenia gravis was reported in 1877 by Samuel Wilks. By 1900 neurologists had described the important clinical characteristics of the disease. At that time, however, diseases were still defined primarily in terms of lesions observed by microscopy at postmortem examination rather than in terms of physiological or etiological factors. In patients with myasthenia, the brain, spinal cord, peripheral nerves, and muscles all appeared normal at autopsy, and the disease was therefore considered a disorder of function.

**Physiological Studies Showed a Disorder of Neuromuscular Transmission**

Two discoveries in the mid 1930s helped to identify myasthenia as a disease of neuromuscular signal transmission. First, Henry Dale, Wilhelm Feldberg, and Marthe Vogt demonstrated that transmission at the neuromuscular junction is mediated by a chemical transmitter that they identified as ACh. Second, Mary Walker found that inhibitors of acetylcholinesterase, such as physostigmine and neostigmine, reverse the symptoms of myasthenia gravis.

In the years between 1945 and 1960 A. McGhee Harvey and his colleagues described in detail the physiological basis of the disorder. When a motor nerve is stimulated electrically, the summed electrical activity of a population of muscle fibers (known as the compound action potential) can be measured with surface electrodes. At stimulation rates of 2–5 per second the amplitude of the compound action potential evoked in normal human muscle remains constant. Harvey found that in myasthenia gravis the amplitude of evoked compound action potentials decreases rapidly. This abnormality resembles the pattern induced in normal muscle by d-tubocurarine (curare), which blocks ACh receptors and inhibits the action of ACh at the neuromuscular junction. Neostigmine (Prostigmin), an inhibitor of
In the 1950s, it was not clear why these tumors were associated with myasthenia or why thymectomy was beneficial, because the immunological role of the thymus was not established until the 1960s. The neurologist John Simpson was one of the first to suggest that myasthenia was an immunological disorder; he pointed out that myasthenia gravis often affects people who have other autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, or Graves disease (hyperthyroidism).

**Identification of Antibodies to the Acetylcholine Receptor Initiated the Modern Period of Research**

The modern concept of myasthenia emerged with the isolation and characterization of the nicotinic ACh receptor. The breakthrough came in 1966. Two chemists, C. C. Chang and C.-Y. Lee, were concerned with a local public health problem in Taiwan—poisonous snake bites. One of the toxins they isolated from snake venom, α-bungarotoxin, was found to cause paralysis by binding essentially irreversibly to ACh receptors at the motor end-plate. By 1971 Lee and Jean-Pierre Changeux in Paris as well as Ricardo Milei and Lincoln Potter in London had used the toxin to isolate and purify ACh receptors from the electric organ of the electric eel.

In 1973 Douglas Fambrough and Daniel Drachman used radioactive α-bungarotoxin to label the ACh receptors in human end-plates. They found fewer binding sites in myasthenic muscle than in controls (Figure 16-3). In the same year James Patrick and Jon Lindstrom injected ACh receptors purified from eel electroplax (which is related to the skeletal muscles of higher vertebrates) into rabbits, intending to use the resulting antibodies to study the properties of eel ACh receptors. Strikingly, the generation of the antibodies was accompanied by the onset of myasthenia-like symptoms in the rabbit. The weakness was reversed by the cholinesterase inhibitors neostigmine or edrophonium. As in humans with myasthenia gravis, the animals were abnormally sensitive to neuromuscular blocking agents, such as curare, and the evoked compound action potentials in muscle decreased with repetitive stimulation. It was later found that a similar syndrome can be induced in mice and other mammals by immunization with ACh receptor protein (Figure 16-4).

By 1975 all the essential characteristics of the human disease had been reproduced in experimental autoimmune myasthenia gravis. These characteristics included a reduction in the amplitude of the miniature end-plate potentials; a smoothing of the normal convor

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**Figure 16-2. Neostigmine increases the duration of action of ACh and thus can compensate for the reduced ACh activity in myasthenia. (From Harvey et al. 1941.)**

A. In a normal person the amplitude of action potentials evoked by a train of four stimuli at 16.6 ms intervals remains constant.  
B. In the myasthenic patient there is a rapid decrease in amplitude.  
C. After injection of 2 mg neostigmine into the brachial artery of the myasthenic patient, the decrease in amplitude was partially reversed.

Cholinesterase that increases the duration of action of ACh at the neuromuscular junction, reverses the decrease in amplitude of evoked compound action potentials in myasthenic patients (Figure 16-2).

**Immunological Studies Indicated That Myasthenia Is an Autoimmune Disease**

Soon after the clinical syndrome had been identified it was recognized that about 15% of adult patients with myasthenia had a benign tumor of the thymus (thymomas). In 1939 Alfred Blalock first reported that the symptoms in myasthenic patients were improved by removal of the thymoma. Based on this finding, Blalock and Harvey, in the 1950s, found that removing the thymus in patients with myasthenia gravis also resulted in a reduction in symptoms, even in the absence of a thymoma. This procedure, known as thymectomy, has become standard treatment for patients with generalized myasthenia gravis.
Figure 16-3 In myasthenia gravis the density of ACh receptors in human muscle fibers is reduced. ACh receptors are marked with 125I-labeled α-bungarotoxin and detected in autoradiograms (drawn here). (Adapted from Fambrough et al. 1973.)

A. In normal fibers there is a dense accumulation of silver grains in a limited junctional area, the end-plate, and a paucity of grains outside this region.

B. In myasthenic fiber the grains are also localized in the end-plate region, but the number per unit area is markedly reduced, indicating a reduced density of functional reactive sites.

Figure 16-4 Posture of a myasthenic mouse before and after treatment with neostigmine. To produce the syndrome the mouse was immunized with 15 μg of ACh receptors from Torpedo californica and received a booster shot 45 days later with 15 μg of the receptor. (From Berman and Patrick 1960.)

A. Before treatment the mouse is inactive.

B. Twelve minutes after receiving an intraperitoneal injection of 37.5 μg/kg neostigmine bromide, the mouse is standing.

lated appearance of the postjunctional folds; loss of ACh receptors from the tips of postjunctional folds (see Figure 16-6); and the deposition at postjunctional sites of antibody and complement, a serum protein that participates in antibody-mediated cell lysis. ACh receptors from electric fish induced experimental autoimmune myasthenia gravis in mice, rats, and monkeys, suggesting that the structure of ACh receptors is highly conserved across species.

After experimental myasthenia gravis was characterized, antibodies directed against ACh receptors were found in the serum of patients with myasthenia. When lymphocytes from patients with myasthenia were cultured, the lymphocytes produced antibodies to ACh receptors. The idea that the human antibodies actually cause the symptoms of myasthenia was also supported by other observations. Repeated injections of serum from patients with myasthenia into mice reproduced the electrophysiological abnormalities in the recipients by reducing the number of available ACh receptors in their end-plates. A similar reduction in ACh receptors occurs with monoclonal antibodies to ACh receptors.

Further support for the role of antibodies against ACh receptors was provided by the detection of antibodies in infants with neonatal myasthenia. These children of myasthenic mothers have difficulty swallowing and their limb movements are impaired. The syndrome lasts from 7 to 10 days; as the symptoms abate, the level of antibodies declines. Similarly, draining lymph from the thoracic lymph ducts improves symptoms of myasthenia in adults. The symptoms recur when the patient’s own lymphatic fluid is injected back into the patient, but not when the patient’s lymphocytes are given separately. The causative factor is therefore in the plasma, rather than a function of the lymphocytes themselves. Furthermore, symptoms improve and antibody levels decline when patients are subjected to plasmapheresis, a procedure in which blood is removed from a patient, cells are separated from plasma, and the cells alone are returned to the patient. The plasma, which contains the antibodies, is discarded.
Figure 16-5  Failure of transmission at the neuromuscular junction in myasthenia gravis. (From Lisak and Barchi, 1982.)

A. In the normal neuromuscular junction the amplitude of the end-plate potential is so large that all fluctuations in the efficiency of transmitter release occur well above the threshold for a muscle action potential (1). Therefore, the amplitude of a compound muscle action potential during repetitive stimulation is constant and invariant (2).

B. In the myasthenic neuromuscular junction, post synaptic changes reduce the amplitude of the end-plate potential in response to presynaptic release of a given amount of ACh, so that under optimal circumstances the end-plate potential may be just sufficient to produce a muscle action potential. Fluctuations in transmitter release that normally accompany repeated stimulation now cause the end-plate potential to drop below this threshold, leading to conduction failure at that junction (3). When the action potential is recorded from the surface of a myasthenic muscle, the amplitude of the compound action potential—a measure of contributions from all fibers in which synaptic transmission is successful—shows a progressive decline and only a small and variable recovery (2) and indicates why the safety factor is reduced in myasthenia.

Immunological Changes Cause the Physiological Abnormality

How do the immunological observations that we have just considered account for the characteristic decrease in the response of myasthenic muscle to repetitive stimulation?

Normally, an action potential in a motor axon releases enough ACh from synaptic vesicles to induce an excitatory end-plate potential with an amplitude of about 70-80 mV (see Chapter 11). Thus the normal end-plate potential is greater than the threshold needed to initiate an action potential, about 45 mV. In normal muscle the difference between the threshold and the actual end-plate potential amplitude—the safety factor—is therefore quite large (Figure 16-5A). In fact, in many muscles the amount of ACh released during synaptic transmission can be reduced by 75%, to as little as 25% of normal before it fails to initiate an action potential.

Most of the ACh released into the synaptic cleft by an action potential is rapidly hydrolyzed by acetylcholinesterase. When the density of ACh receptors is reduced, as it is in myasthenia, the probability that a molecule of ACh will find a receptor before it is hydrolyzed is reduced. Moreover, the geometry of the end-plate is also disturbed in myasthenia. The normal infolding at the junctional folds is reduced and the synaptic cleft is enlarged (Figure 16-6). These morphological changes increase the diffusion of ACh away from the synaptic cleft and thus further reduce the probability of ACh interacting with the few remaining functional receptors. As a result, the amplitude of the end-plate potential is reduced to the point where it is barely above threshold (Figure 16-5B). Thus, transmission is readily blocked even though the vesicles in the presynaptic terminals contain normal amounts of ACh and the processes of exocytosis and release are intact. Both the physiological abnormality (the decremental response) and the clinical symptoms (muscle weakness) are partially reversed by drugs that inhibit active cholinesterase because the released ACh molecules remain unhydrolyzed for a longer time, and this increases the probability that they will interact with receptors.

The reduced efficacy of neuromuscular transmission in myasthenia can be assessed by the clinical tec-
Antibody Binds to the α-Subunit of the Acetylcholine Receptor in Myasthenia Gravis

As discussed in Chapter 11, the genes for each of the subunits of mammalian ACh receptor have been cloned and sequenced, and peptides corresponding to specific domains of ACh receptor subunits have been synthesized. In experimental animals antibodies that cause myasthenia are usually active against either of two peptide sequences on the native receptor—the bungarotoxin-binding site or an area on the α-subunit called the main immunogenic region. Circulating antibodies in humans are often directed against the main immunogenic region.

Even though it has been well established that antibodies to the α-subunit of ACh receptors have a central role in the pathogenesis of myasthenia—so much so that myasthenia is now the prototype of human autoimmune disease—several questions remain unanswered. What, for example, initiates the production of antibodies to the ACh receptor? One possibility is that persistent viral infection could alter the properties of the surface membrane, rendering it immunogenic, but this has not been shown. Another possibility is that viral or bacterial antigens may share epitopes with the ACh receptor. Thus, when a person is infected, the antibodies generated against the foreign organism may also recognize the ACh receptor. The molecular similarity of the antigens is called molecular mimicry.

How do antibodies cause the symptoms of myasthenia? The antibodies do not occupy the receptor site alone. This conclusion emanates from the test used to detect antireceptor antibodies in human serum. The circulating antibodies will even react with purified ACh receptors that have been labeled with radioactive α-bungarotoxin. Because the toxin itself occupies and blocks the ligand binding site, the antibody must react with epitopes elsewhere on the receptor molecule.

One effect of the antibodies might be to interfere with the interaction of ACh and the receptor. The loss of receptors is, however, probably due to an increase in turnover and degradation of ACh receptors. Myasthenic antibodies are able to bind and cross-link ACh receptors, in this way triggering the internalization and degradation of the receptor (Figure 16-7). In addition, some antibodies to ACh receptors in myasthenic patients bind proteins of the complement cascade, which may result in lysis of the postsynaptic membrane.

Although the evidence implicating ACh receptor antibodies in myasthenic symptoms is compelling, the antibodies are not found in all myasthenic patients. Moreover, there is no consistent relationship between the serum concentration of antibodies directed against ACh receptors and the severity of symptoms. One explanation of this dissociation is that the antibodies found in the serum of myasthenic patients or in animals...
with experimentally induced myasthenia gravis are polyclonal; they are produced by different B cells in response to different antigenic determinants, and therefore the serum of each patient contains antibodies with distinct specificities. As a consequence, some people with high titers of antibodies to the receptor but few or no clinical symptoms might have a type of antibody that is limited in its ability to interfere with synaptic transmission or to influence ACh receptor turnover. In contrast, other patients with severe myasthenia might have low titers of antibodies that are effective in interfering with the function of the receptor and its turnover.

### The Molecular Basis of the Autoimmune Reaction Has Been Defined

The autoimmune reaction depends on interactions within a trimolecular complex comprising the following: (1) the antigen, the immunogenic peptide of the ACh receptor or a peptide that mimics the receptor; (2) an antigen-specific T-cell receptor; and (3) class II molecules of the major histocompatibility complex (MHC) that are expressed on the antigen-presenting cell (Figure 16-8A). The T cells become reactive against the ACh receptor. This could result from an infection in which a viral protein includes a peptide homologous to one in the ACh receptor, a form of molecular mimicry. Once activated, the T cells could recognize the ACh receptor on myoid cells in the thymus. Antigen-specific T cells have actually been identified in the thymus glands of patients with myasthenia.

The class II MHC genes also play a major role in determining susceptibility. Patients with myasthenia gravis have more of the histocompatibility subtypes DR3 and DQ2. The relative risk of people with human leukocyte antigen (HLA)–DQ for myasthenia is three times more than that of people with other HLA haplotypes.
The specific immunogenic peptides of human ACh receptors have also been identified.

These findings open new approaches to therapy for patients who do not improve sufficiently with anticholinesterase drug therapy or thymectomy. For instance, it might be possible to make antibodies against the anti-ACh receptor antibodies or anti-idiotypic antibodies. However, this has proven difficult in experimental myasthenia. Another approach is to develop peptide competitors for ACh receptors that might block T-cell recognition of ACh receptors or MHC binding of ACh receptor fragments (Figure 16-8B). Alternatively, anti-
bodies might be developed against either MHC class II molecules of the antigen-presenting cells or receptors on the T cells that recognize ACh receptors.

Current Therapy for Autoimmune Myasthenia Gravis Is Effective But Not Ideal

Treatment of a patient with myasthenia is based upon the altered physiology and the autoimmune pathogenesis. Anticholinesterases, especially pyridostigmine, are used to provide symptomatic relief but this is rarely complete and does not alter the basic disease. Immunosuppressive therapies include corticosteroids and azathioprine or related drugs that suppress antibody synthesis. Plasmapheresis, removing the plasma and the antibodies to the ACh receptor, often ameliorates symptoms within days or a few weeks, but the benefit is transient. The temporary benefit may be sufficient to prepare a patient for thymectomy or to support the patient through more severe episodes. Intravenous administration of immunoglobulins also reduces the titer of antibodies to the ACh receptor by mechanisms that are not clear.

Twenty-five years ago the mortality rate of myasthenia was about 33%. Now, few patients die of the disease and life expectancy is almost normal. This change is largely due to advances in intensive care, including mechanical ventilation and antibiotics. Years ago respiratory-care units of hospitals were populated by many patients in myasthenic “crisis,” defined by the use of a mechanical ventilator for a patient in respiratory distress. Now the number of patients in crisis has declined drastically. Many investigators attribute this change to the practice of thymectomy. After thymectomy about half of the patients are in “remission”—they have no symptoms of myasthenia and take no drugs. It is not clear how thymectomy is beneficial; it removes a source of antigen (ACh receptors are present on the myoid cells found in normal thymus), and it also removes a major source of lymphocytes that synthesize the antibodies. The thymus must also play a role in immunoregulation, including the pathophysiology of myasthenia gravis. Further improvement in therapy will have to be directed toward patients who are not helped by thymectomy.

Congenital Forms of Myasthenia Gravis

It had long been recognized that symptoms of myasthenia may be present from birth. Congenital myasthenia differs from neonatal myasthenia; in the neonatal syn-
In contrast, ACh receptors, as visualized by labeling with radioactive bungarotoxin, are preserved.

The **slow-channel syndrome** is characterized by prominent limb weakness with little weakness of cranial muscles (the reverse of the pattern usually seen in autoimmune myasthenia, where muscles of the eyes and oropharynx are almost always affected). The end-plate potentials of the slow-channel syndrome are prolonged in a manner similar to that observed in AChE deficiency, and spontaneous miniature end-plate potentials are also prolonged. In contrast, however, AChE is present and shows normal kinetics. These features suggest that the opening of the ACh receptor channel is abnormally prolonged. In addition, miniature end-plate potentials are of abnormally low amplitude, which could result from the degeneration of junctional folds and loss of ACh receptors.

It is not certain how the slow-channel syndrome arises. However, the ACh receptor-channel is similarly slow in newly formed end-plates in normal mammalian muscle. It is possible that the developmental transition from slow to fast channels (which is accompanied by replacement of the γ-subunit of the ACh receptor by an ε-subunit) is prevented. It is also possible that a mutation has altered the ACh receptor in a way that modifies the time the channel spends in the open state.

Because the genes for all its subunits have been cloned, it is now possible to identify the specific mutations of the ACh receptor. This has not yet been achieved, but progress is being made. For instance, immunocytochemical analysis has revealed the absence of the long cytoplasmic loop of the ε-subunit in one form of congenital myasthenia. Molecular DNA analysis tends to confirm this interpretation.

Anticholinesterase inhibitors are effective in some of these disorders, not in others. Some patients seem to benefit from 3,4-diaminopyridine, which blocks K⁺ conductance and promotes the release of ACh at nerve terminals.

**Other Disorders of Neuromuscular Transmission: Lambert-Eaton Syndrome and Botulism**

Some patients with cancer, especially small-cell cancer of the lung, have a syndrome of proximal limb weakness and a neuromuscular disorder with characteristics that are opposite of those seen in myasthenia gravis. Instead of a decline in synaptic response to repetitive nerve stimulation, the amplitude of the evoked potential increases, a state called **facilitating neuromuscular block**. Here the first postsynaptic potential is abnormally small, but subsequent responses increase in amplitude so that the final summed potential produced by a train of five spikes per second is two to four times the amplitude of the first potential. This disorder, the Lambert-Eaton syndrome, is attributed to the action of antibodies against voltage-gated Ca²⁺ channels in the presynaptic terminals.

It has not yet been possible to identify which subtype of Ca²⁺ channel is affected, but an assay has been developed with the ligand α-conotoxin, which is isolated from a snail and binds to the N-type channel. Serum from patients with the syndrome binds to the α-conotoxin receptor. Although the assay is convenient and sensitive, it is not specific and there are many false positive responses in people who do not have the Lambert-Eaton syndrome. Also, serum from patients reacts with L-, T-, and P-type voltage-gated Ca²⁺ channels. Nevertheless, it is thought that the antibody reacts with an antigen in the channel and that, in parallel with the process in myasthenia, the antibody-antigen complex is internalized and the receptors are degraded. Similar Ca²⁺ channels are found in cultured cells from the small-cell carcinoma of the lung; development of antibodies against these antigens in the tumor might be followed by pathogenic action against nerve terminals, another kind of molecular mimicry.

This theory emerged from passive transfer experiments. Mice injected with serum from Lambert-Eaton patients showed electrophysiological abnormalities typical of the human syndrome; electron microscope evidence showed loss of the presynaptic active zones and active zone particles thought to be Ca²⁺ channels (see Chapter 13). Loss of the voltage-gated Ca²⁺ channels at the active zones would be expected to reduce the entry of Ca²⁺ when nerve terminals are depolarized, impairing the release of transmitter.

Confirmation of the autoimmune theory has come from therapeutic responses of the patients to plasmapheresis, intravenous immunoglobulin therapy, and long-term immunosuppressive drug therapy. In some patients the neurological disorder has disappeared with successful treatment of the cancer. Some patients with the Lambert-Eaton syndrome have no recognized tumor, even at autopsy. In these patients the pathogenesis is not known.

A similar facilitating neuromuscular block is found in human botulism; the botulinum toxin also impairs release of ACh from nerve terminals. Both botulism and the Lambert-Eaton syndrome are ameliorated by administration of calcium gluconate or guanidine, agents that promote the release of ACh, but these drugs are less effective than immunosuppressive treatments for long-term control of the Lambert-Eaton syndrome, which is chronic. Botulism, on the other hand, is transient, and if the patient...
is kept alive during the acute phase by treating symptoms, the disorder disappears in weeks as the infection is controlled and botulinum toxin is inactivated.

An Overall View

Studies of autoimmune myasthenia, congenital myasthenia, and the Lambert-Eaton syndrome are good examples of the useful synergy between clinical and basic neuroscience, and the fruitful interactions of both approaches with molecular genetics and molecular immunology. All three of these illnesses have been elucidated by advances in basic science. In turn, the clinical disorders have provided information about the normal structure and function of the neuromuscular junction. A combination of clinical and basic science has also led to more effective therapy. Nevertheless, the symptoms of these diseases cannot always be alleviated and some patients remain disabled, so more advances through research are essential.

Lewis P. Rowland

Selected Readings


References


