461 Myasthenia Gravis and Other Diseases of the Neuromuscular Junction

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Myasthenia gravis (MG) is a neuromuscular disorder characterized by weakness and fatigability of skeletal muscles. The underlying defect is a decrease in the number of available acetylcholine receptors (AChRs) at neuromuscular junctions due to an antibody-mediated autoimmune attack. Treatment now available for MG is highly effective, although a specific cure has remained elusive.

PATHOPHYSIOLOGY

At the neuromuscular junction (Fig. 461-1, Video 461-1), acetylcholine (ACh) is synthesized in the motor nerve terminal and stored in vesicles (quanta). When an action potential travels down a motor nerve and reaches the nerve terminal, ACh from 150 to 200 vesicles is released and combines with AChRs that are densely packed at the peaks of postsynaptic folds. The AChR consists of five subunits (2α, 1β, 1δ, and 1γ or ε) arranged around a central pore. When ACh combines with the binding sites on the α subunits of the AChR, the channel in the AChR opens, permitting the rapid entry of cations, chiefly sodium, which produces depolarization at the end-plate region of the muscle fiber. If the depolarization is sufficiently large, it initiates an action potential that is propagated along the muscle fiber, triggering muscle contraction. This process is rapidly terminated by hydrolysis of ACh by acetylcholinesterase (AChE), which is present within the synaptic folds, and by diffusion of ACh away from the receptor.

In MG, the fundamental defect is a decrease in the number of available AChRs at the postsynaptic muscle membrane. In addition, the postsynaptic folds are flattened, or "simplified." These changes result in decreased efficiency of neuromuscular transmission. Therefore, although ACh is released normally, it produces small end-plate potentials that may fail to trigger muscle action potentials. Failure of transmission at many neuromuscular junctions results in weakness of muscle contraction.

The amount of ACh released per impulse normally declines on repeated activity (termed *presynaptic rundown*). In the myasthenic patient, the decreased efficiency of neuromuscular transmission combined with the normal rundown results in the activation of fewer and fewer muscle fibers by successive nerve impulses and hence increasing weakness, or *myasthenic fatigue*. This mechanism also accounts for the decremental response to repetitive nerve stimulation seen on electrodiagnostic testing.

The neuromuscular abnormalities in MG are caused by an autoimmune response mediated by specific anti-AChR antibodies. The anti-AChR antibodies reduce the number of available AChRs at neuromuscular junctions by three distinct mechanisms: (1) accelerated turnover of AChRs by a mechanism involving cross-linking and rapid endocytosis of the receptors; (2) damage to the postsynaptic muscle membrane by the antibody in collaboration with complement; and (3) blockade of the active site of the AChR, i.e., the site that normally binds ACh. An immune response to muscle-specific kinase (MuSK), a protein involved in AChR clustering at neuromuscular junctions, can also result in MG, with reduction of AChRs demonstrated experimentally. Anti-MuSK antibody occurs in about 40% of patients without AChR antibody. A small proportion of patients whose sera are negative for both AChR and MuSK antibodies have antibodies to another protein at the neuromuscular junction—low-density lipoprotein receptor-related protein 4 (lrp4)—that is important for clustering of AChRs. The pathogenic antibodies are IgG and are T cell dependent. Thus, immunotherapeutic strategies directed against either the antibody-producing B cells or helper T cells are effective in this antibody-mediated disease.

How the autoimmune response is initiated and maintained in MG is not completely understood, but the thymus appears to play a role in this process. The thymus is abnormal in ~75% of patients with AChR antibody–positive MG; in ~65% the thymus is "hyperplastic," with the presence of active germinal centers detected histologically, although the hyperplastic thymus is not necessarily enlarged. An additional 10% of patients have thymic tumors (thymomas). Muscle-like cells within the thymus (myoid cells), which express AChRs on their surface, may serve as a source of autoantigen and trigger the autoimmune reaction within the thymus gland.

CLINICAL FEATURES

MG is not rare, having a prevalence as high as 2–7 in 10,000. It affects individuals in all age groups, but peaks of incidence occur in women in their twenties and thirties and in men in their fifties and sixties. Overall, women are affected more frequently than men, in a ratio of ~3:2. The cardinal features are *weakness* and *fatigability* of muscles. The weakness increases during repeated use (fatigue) or late in the day and may improve following rest or sleep. The course of MG is often variable. Exacerbations and remissions may occur, particularly during the first few years after the onset of the disease. Remissions are rarely complete or permanent. Unrelated infections or systemic disorders can lead to increased myasthenic weakness and may precipitate "crisis" (see below).

The distribution of muscle weakness often has a characteristic pattern. The cranial muscles, particularly the lids and extraocular muscles, are typically involved early in the course of MG; diplopia and ptosis are common initial complaints. Facial weakness produces a "snarling" expression when the patient attempts to smile. Weakness in chewing is most noticeable after prolonged effort, as in chewing meat. Speech may have a nasal timbre caused by weakness of the palate or a dysarthric "mushy" quality due to tongue weakness. Difficulty in swallowing may occur as a result of weakness of the palate, tongue, or pharynx, giving rise to nasal regurgitation or aspiration of liquids or food. Bulbar weakness is especially prominent in MuSK antibody–positive MG. In ~85% of

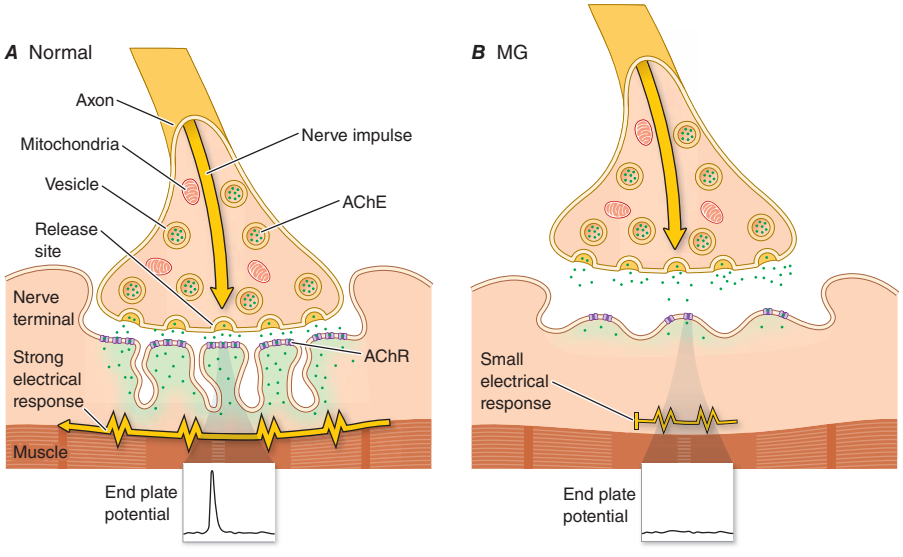

FIGURE 461-1 Diagrams of (*A*) normal and (*B*) myasthenic neuromuscular junctions. AChE, acetylcholinesterase. See text for description of normal neuromuscular transmission. The myasthenia gravis (MG) junction demonstrates a normal nerve terminal; a reduced number of acetylcholine receptors (AChRs) (stippling); flattened, simplified postsynaptic folds; and a widened synaptic space. **See Video 461-1 also.** *(Modified from DB Drachman: N Engl J Med 330:1797, 1994; with permission.)*