Myasthenia gravis

Myasthenia gravis (MG) is a neuromuscular junction (NMJ) disorder characterized by weakness and fatigability of skeletal muscles. The underlying defect is a decrease in the number of available acetylcholine receptors (AChRs) at NMJs **due to an antibody-mediated autoimmune attack.**

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 **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 eyelid, external ocular, facial and pharyngeal muscles are generally involved first. Later, limb and respiratory muscles get affected.

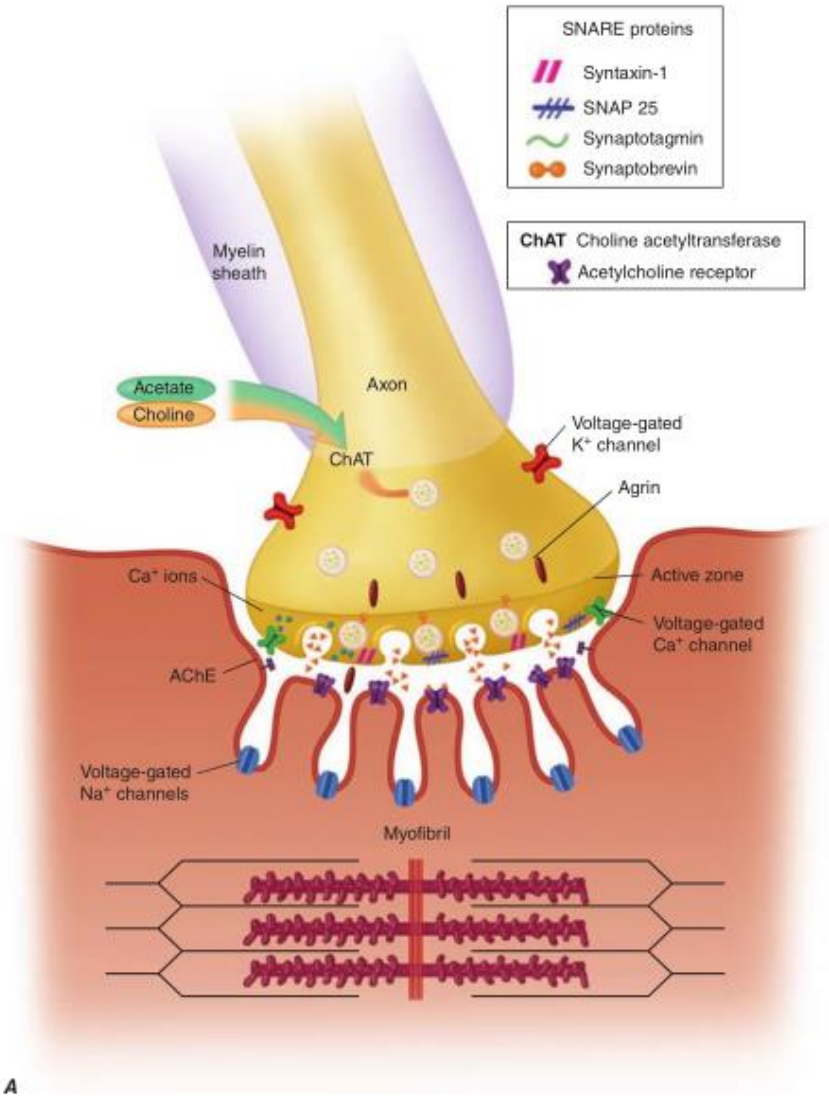

FIGURE 440-1 Illustrations of (*A*) a normal presynaptic neuromuscular junction, (*B*) a normal postsynapatic terminal, and (*C*) a myasthenic neuromuscular junction. AChE, acetylcholinesterase. See text for description of normal neuromuscular transmission. The myasthenia gravis (MG) junction demonstrates a reduced number of acetylcholine receptors (AChRs); flattened, simplified postsynaptic folds; and a widened synaptic space. See Video 440-1 also. *(From AA Amato, J Russell: Neuromuscular Disorders, 2nd ed. New York, McGraw-Hill, 2016, Figures 25-3 [p 588], 25-4 [p 589], and 25-5 [p 590]; with permission.)*

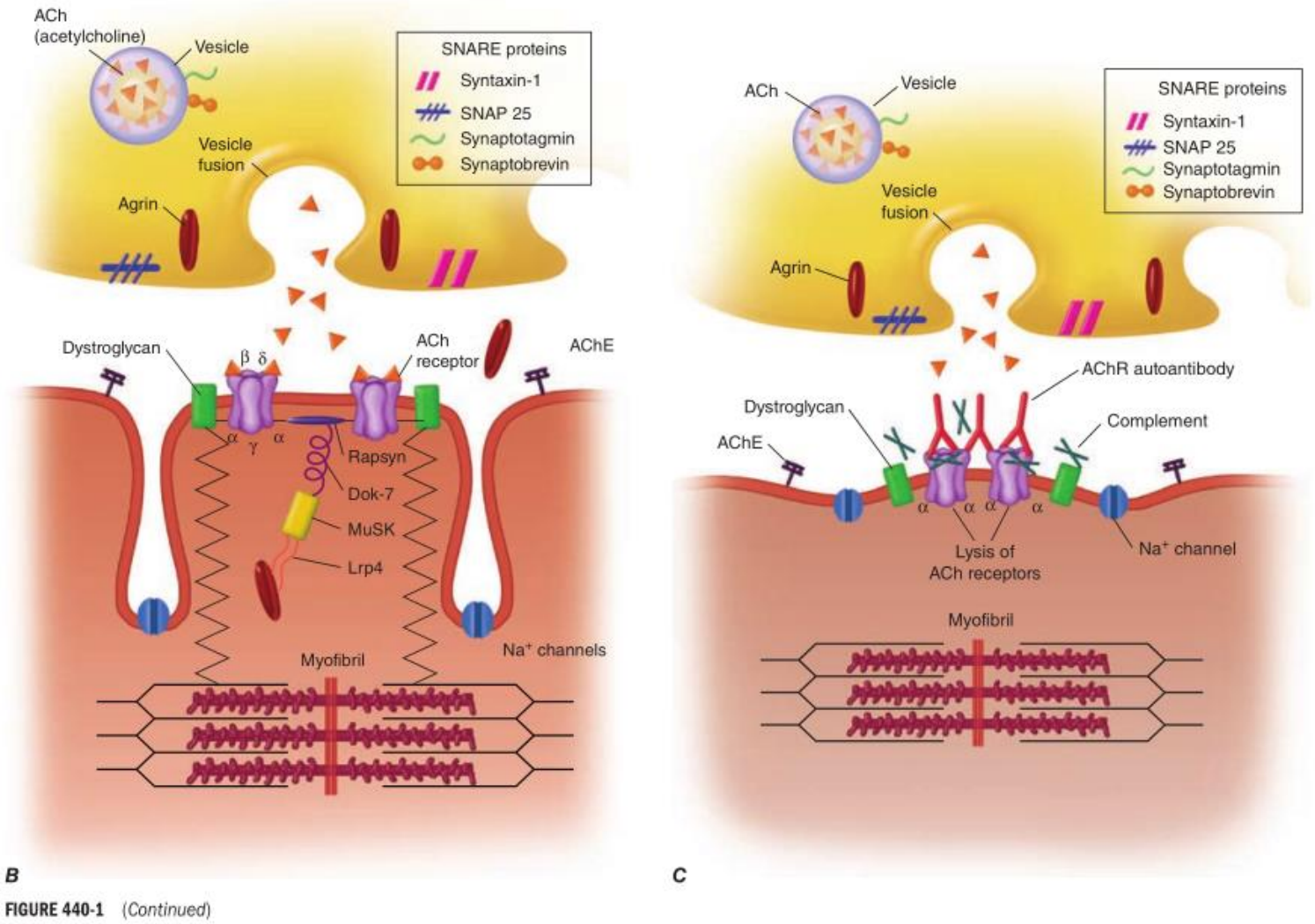

FIGURE 440-1 *(Continued)*

Diagnostic tests for myasthenia gravis

(a) **Ameliorative test**: Initially edrophonium 2 mg is injected i.v. as a test dose. If nothing untoward happens, the remaining 8 mg is injected after 30–60 sec. Reversal of weakness and shortlasting improvement in the strength of affected muscles occurs only in myasthenia gravis and not in other muscular dystrophies.

In case edrophonium is not available, the test can be performed with 1.5 mg i.v. neostigmine.

Atropine pretreatment may be given to block the muscarinic effects of neostigmine.

(b) **Provocative test**: myasthenics are highly sensitive to d-tubocurarine; 0.5 mg i.v. causes marked weakness in them

but is ineffective in non-myasthenics. This test is hazardous: facilities for positive pressure respiration must be at hand

before performing it. This test is better not performed.

(c) **Demonstration of anti-NR antibodies** in plasma or muscle biopsy specimen is a more reliable test.

Treatment

- Neostigmine and its congeners improve muscle contraction by allowing Ach released from prejunctional endings to accumulate and act on the receptors over a larger area, as well as by directly depolarizing the endplate.
- Treatment is usually **started with neostigmine 15 mg orally every 6 hours**; dose and frequency is then adjusted to obtain optimum relief from weakness. However, the dosage requirement may fluctuate from time to time and there are often

unpredictable periods of remission and exacerbation**. Pyridostigmine is an alternative** which needs less frequent dosing. If intolerable muscarinic side effects are produced, atropine can be added to block them.

- These **drugs have no effect on the basic disorder** which **often progresses**; ultimately it may not be possible to restore muscle strength adequately with anti-ChEs alone. Corticosteroids afford considerable improvement in such cases by their immunosuppressant action. They inhibit production of NR-antibodies and may increase synthesis of NRs.
- However, their long term use has problems of its own. **Prednisolone 30–60 mg/day induces remission in about 80% of the advanced cases; 10 mg daily or on alternate days can be used for maintenance therapy.** Other immunosuppressants have also been used with benefit in advanced cases. Both azathioprine and cyclosporine also inhibit NR-antibody synthesis by affecting T-cells, but response to the former is slow in onset (takes up to 1 year), while that to the latter is relatively quick (in 1–2 months).
- **Removal of antibodies by plasmapheresis (plasma exchange) is another therapeutic approach**. Dramatic but short-lived improvement can often be achieved by it in myasthenic crisis.
- **Thymectomy is effective in a majority of the cases*. It produces gradual improvement and even complete remission has been obtained***. Thymus may contain modified muscle cells with NRs on their surface, which may be the source of the antigen for production of anti-NR antibodies in myasthenic patients.
- Myasthenic crisis is characterized by acute weakness of respiratory muscles. It is managed by tracheal intubation and mechanical ventilation. Generally, i.v. methylprednisolone pulse therapy is given while anti-ChEs are withheld for 2–3 days followed by their gradual reintroduction.
- Most patients can be weaned off the ventilator in 1–3 weeks. Plasmapheresis hastens recovery. Overtreatment with anti-ChEs If the dose of the antiChE is not adjusted according to the fluctuating requirement, relative overdose may occur from time-to-time. Overdose also produces weakness by causing persistent depolarization of muscle endplate, and is called cholinergic weakness. Late cases with high anti-ChE dose requirements often alternately experience myasthenic and cholinergic weakness and these may assume crisis proportions. The two types of weakness require opposite treatments.
- **They can be differentiated by edrophonium test**