Myasthenia gravis: An Autoimmune Response against the Acetylcholine Receptor

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Abstract
Myasthenia gravis (MG) is an organ-specific autoimmune disease caused by an antibody-mediated assault on the muscle nicotinic acetylcholine receptor (AChR) at the neuromuscular junction. Binding of antibodies to the AChR leads to loss of functional AChRs and impairs the neuromuscular signal transmission, resulting in muscular weakness. Although a great deal of information on the immunopathological mechanisms involved in AChR destruction exists due to well-characterized animal models, it is not known which etiological factors determine the susceptibility for the disease. This review gives an overview of the literature on the AChR, MG and experimental models for this autoimmune disease.

Introduction
Myasthenia gravis (MG) is an organ-specific autoimmune disease that results from an antibody-mediated assault on the muscle nicotinic acetylcholine receptor (AChR) at the neuromuscular junction [1]. Binding of antibodies to the AChR leads to loss of functional AChRs and impairs the neuromuscular signal transmission, resulting in muscular weakness. Although MG is a rare disease with an annual incidence of about 4 per million, it is one of the best-studied autoimmune diseases. The disease is exemplary for autoantibody-mediated target tissue injury. Our understanding of the pathogenesis of MG is considerably enhanced because of the molecular characterization of the AChR and the presence of a well-characterized animal model: experimental autoimmune MG (EAMG) [2, 3]. This experimental model is induced by immunization of rodents with purified AChR or passive transfer of anti-AChR antibodies into these animals. The EAMG model resembles human MG in many respects [1]. Although a great deal of information exists about the immunopathological mechanisms involved in AChR destruction, it is not known what etiological...
factors determine the susceptibility for the disease. This review gives an overview of the literature about the AChR, MG and experimental models for this autoimmune disease.

**The Acetylcholine Receptor**

In 1936 Dale et al [4] demonstrated that stimulated nerve-muscle preparations produced acetylcholine and that this substance caused contractions in muscle preparations. The notion of a specific AChR protein was next postulated by Nachmansohn [5] in 1952. Discovery of α-neurotoxins, in particular α-bungarotoxin from the venom of *Bungarus multicinctus* made it possible to define the nature of the receptor [6]. Isolation of the receptor from the electric organs of *Torpedo californica* was first achieved in the early seventies by several investigators using α-toxins [7–10]. Patrick and Lindstrom [11] further characterized the AChR which led to the observation that MG was caused by an autoimmune response against the AChR. In the next decade monoclonal antibodies were used to define important pathogenic epitopes, and the use of molecular biology has revealed much information about the structure and function of the AChR.

**Structure and Function of the AChR**

The transmission of impulses from nerve to muscle depends on release of acetylcholine from the motor nerve ending and subsequent interaction with the AChR. Binding of acetylcholine to the AChR opens the AChR ion channel, allowing Na+ ions to enter and to depolarize the muscle membrane, leading to contraction of the muscle. AChRs are located in the postsynaptic membrane at the neuromuscular junction. The postsynaptic membrane has deep infoldings that increase the surface area up to 10 times the length of the presynaptic membrane [12, 13]. The AChR is situated at the top of these folds at a high density of 8,000–10,000 molecules/μm² [14, 15].

The amount of AChR in mammalian skeletal muscle is about 10 μg/kg. The electric organs of *T. californica* and other electric rays and eels, however, provide a richer source of AChR. The electroplax tissue contains approximately 100 mg/kg AChR and therefore was the starting point for purification and characterization of the receptor. Since the AChR is an evolutionary well-conserved molecule, much information obtained from these fish AChRs can be applied to mammalian skeletal muscle [16, 17]. Information about the structural and functional properties of the AChR has been obtained from sequence analysis of the genes that code for the AChR subunits. At present the AChR genes have been sequenced from Torpedo, the calf, rat, mouse, chicken [18] and human [19–22]. The homology between Torpedo and mammalian AChRs (calf) is about 80% for the α-subunit and 55% for the other subunits [23–26].

The AChR of electric fish is a transmembrane protein composed of four different subunits in a stoichiometry αβγδ [27–31]. The apparent and calculated protein molecular weights of these subunits from Torpedo AChR are: α, 38,000 and 50,116; β, 49,000 and 53,681; γ, 57,000 and 56,279; δ, 64,000 and 57,565 dalton [16]. The AChR molecule is approximately 125 Å long of which the extracellular domain protrudes 55 Å above the membrane and the intracellular domain extends 15 Å below the membrane [17]. From above AChRs are seen as 85-Ångström diameter ring-like structures protruding from the membrane [18, 19]. The independent subunits have considerable amino acid sequence homology as a consequence of their evolution from a common ancestor by gene duplication [16]. Therefore, the structure and transmembrane orientation are similar between the dif-