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# THE PATHOGENESIS OF MYASTHENIA GRAVIS

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# Abstract

The identification and purification of the acetylcholine receptor molecule has permitted a major advance in understanding the pathogenesis of Myasthenia gravis. The author explains the central role of the receptor and its connections with the main features of the disease. He gives a description of the pathogenic mechanisms involved.

### Résumé

L'identification et la caractérisation du récepteur de l'acétylcholine ont permis de réaliser d'importants progrès dans la compréhension de la pathogenèse de la myasthénie grave. L'auteur passe en revue les liens existant entre le récepteur de l'acétylcholine et les principales caractéristiques anatomocliniques de la myasthénie grave. Il donne un aperçu des mécanismes pathogéniques tels qu'ils sont envisagés actuellement.

Myasthenia gravis has four main characteristics:

- 1) Muscle weakness and fatigability caused by defective neuromuscular transmission,
- 2) Autoantibodies directed against skeletal muscle antigens,
- 3) Pathological changes within the thymus,
- Genetic linkage of the disease susceptibility to the major histocompatibility gene complex (HLA).

The important progresses made recently in understanding the mechanisms of the defective neuromuscular transmission observed in Myasthenia gravis have been made possible by detailed studies of the function and molecular organization of the neuromuscular junction (for a review see 1).

It is now widely admitted that the transmission of the excitation from a nerve to a muscle occurs in the following way. Impulses are generated on skeletal muscle fibers when they

are depolarized beyond a critical threshold. These impulses propagate along the whole muscle fiber and cause its contraction to occur. Under physiological conditions, the primary event measurable on the muscle side, the "graded" depolarization, results from an indirect activation of the muscle fiber through the motor nerve. Actually, when an action potential reaches and depolarizes a motor nerve terminal, it triggers the secretion of roughly 500'000 acetylcholine (AcCh) molecules into the synaptic cleft. These molecules reach the muscle fiber membrane where some are hydrolyzed at once by an enzyme, the acetylcholinesterase, while others react in a reversible manner on a specific recognition site: the acetylcholine receptor (AcChR). This interaction of AcCh molecules with AcChR's is assumed to modify, in a still unknown manner, the properties of the postsynaptic part of the muscle fiber membrane which thereby becomes transiently permeable to the ions located on both its sides.

Although the sequence of events underlying the specific effect of AcCh molecules on the ionic conductances of the muscle fiber membrane is still not completely known, several individual components, however, have been well characterized. One of them is AcChR. Originally the concept of an AcCh receptive substance rested on the only physiological response to AcCh. As a matter of fact, it referred to an hypothetical macromolecule located on the postsynaptic membrane and having with AcCh a transitory interaction connected, through many steps, to a measurable cellular response. This biochemical concept became recently a biochemical reality: an "integral" membranar glycoprotein whose exact molecular weight, subunit composition and tridimensional organization are still under intensive study (for a review see 2). This was made possible by the discovery (3) of neurotoxins with specific curare-like actions and kinetic properties favorable for assaying AcChR both in situ and in solution. These neurotoxins are found in rather large quantities in the venom of certain snakes. One is α-bungarotoxin (α-Bgt), a small protein of about 8'000 daltons that can be radioactively labelled with either <sup>3</sup>H or <sup>125</sup>I without loss of biological activity.

The availability of  $\alpha$ -Bgt allowed also a precise estimate of the number and distribution of AcChR's in the human neuromuscular junction. In 1973, FAMBROUGH et al. (4), using 125 I-labelled  $\alpha$ -Bgt and autoradiographic techniques showed an 80 % reduction in the number of AcChR's detectable in the neuromuscular junction of myasthenic patients. At that time, the exact site and nature of the neuromuscular defect observed in Myasthenia gravis were still controversial. There had been considerable debate as to whether the nerve terminal, the postsynaptic region of the muscle, or both, were affected. The findings of FAMBROUGH et al. were considered as strong arguments in favor of a receptor disorder in Myasthenia gravis. A great number of experiments were then designed in several laboratories in order to test this hypothesis.

Four years later, there are enough experimental evidences indicating that Myasthenia gravis might well be caused by an autoimmune reaction to AcChR. This confirms an hypothesis advanced by SIMPSON in 1960 (5) according to which there are in Myasthenia gravis, "antibodies to an end-plate protein with the properties of an AcCh competitive substance". The most striking evidences indicating that AcChR is involved in the pathogenesis of the neuromuscular defect observed in Myasthenia gravis are listed below:

- a) There is a reduction
  - i) in the absolute number of AcChR's revealed in the neuromuscular junctions of myasthenic patients by means of <sup>125</sup> I-labelled α-Bgt and autoradiographic techniques (4);
  - ii) in the surface of the postsynaptic membrane containing AcChR's available for  $\alpha$ -Bgt binding (6).
- b) There are anti-AcChR antibodies in the serum of myasthenic patients.

  These antibodies are directed predominantly against determinants other than the AcCh binding site. It was first shown that serum factors could block the binding of 125 I-label-led α-Bgt, both in vitro to solubilized AcChR from denervated rat muscles (7), and in situ to intact AcChR on tissue sections from normal human neuromuscular junctions (8). Later, these factors were identified as immunoglobulins G (9). Anti-AcChR antibodies have also been shown to exist in the blood of babies with neonatal Myasthenia gravis (10) and in the cerebrospinal fluid of myasthenic patients (11).
- c) Molecules the size of antibodies have been shown to reach AcChR in situ (12). Moreover immune complexes have been revealed at the endplate of myasthenic patients (13). The distribution of these complexes is similar to the one of AcChR's on the postsynaptic membrane.
- d) It is possible to obtain animal models sharing similarities with human Myasthenia gravis
  - i) by injection of sublethal doses of neurotoxins inhibiting specifically AcChR (14, 15);
  - by injection of immunoglobulins G from patients with Myasthenia gravis (16);
  - iii) by immunization with AcChR purified either from the electric organs of certain fishes or from rat denervated muscles (17, 18, 19, 20). The immunized animals show muscle weakness due to impaired neuromuscular transmission. They have also high levels of anti-AcChR antibodies in their serum. These antibodies are also present in the cerebrospinal fluid (21). When these antibodies are injected to healthy animals, the recipients develop the disease (22).
- e) There is an accelerated AcChR degradation by cultured rat skeletal muscle cells when immunoglobulins from myasthenic patients are added to the culture medium (23, 24).

This increased rate of degradation results in a lowered AcChR's density on the muscle cell membranes.

f) There is a reduced AcChR sensitivity to iontophoretically applied AcCh in cultured muscle cells or myotubes from rat and man when immunoglobulins from myasthenic patients are added to the culture medium (23, 25, 26).

These observations indicate that the defect in the neuromuscular transmission observed in Myasthenia gravis can be explained by an AcChR functional deficiency at the myasthenic endplate. The three following mechanisms could contribute to this synaptic dysfunction, but the importance of their relative contribution is still debated (13):

- 1. A pure immunopharmacologic blockade of AcChR. This would imply antibodies competing for the AcCh binding site and for antibodies inhibiting (either sterically or allosterically) the interaction of AcChR with the neurotransmitter (27).
- 2. A destruction of AcChR containing segments of the postsynaptic membrane consecutive to the binding of antibodies to AcChR. There are, actually, evidences that such a binding results in completion of the activation phase of the complement reaction (13). The possibility that some complement fixing immunologic system might be implicated in the pathogenesis of Myasthenia gravis was first raised in 1960 by STRAUSS et al. (28).
- 3. An accelerated internalization and intracellular degradation (modulation) of the AcChRantibody complex. One has to keep in mind, however, that this mechanism has been shown to occur only on cultured cells.

As mentioned above, two of the main characteristics of Myasthenia gravis (defective neuro-muscular transmission and autoantibodies directed against muscle antigens) are compatible with a central role for AcChR in the pathogenesis of the disease. Recent studies have shown that the role of the receptor could also explain the third characteristic of the disease: the thymus involvement. In this respect, clinical pathological evidences include a high incidence of thymic hyperplasia (65 %) and neoplasia (10 %) as well as beneficial effect of thymectomy. As a matter of fact, extracts of thymic tissue have been shown to contain AcChR (29, 30). It was known for a long time that some muscle-like cells, called "myoid cells", were present in the thymus. Hypotheses were advanced concerning their role in Myasthenia gravis (31) and the possibility of finding AcChR on them (32). Recently specific thymic cells bearing AcChR were identified in culture (33, 34). They were obtained from dissociated healthy thymuses. These cells are identical to skeletal muscle cells with respect to morphology, contractility and electrophysiological properties. AcChR was also detected on the epithelial cells of human thymus. These cells were found to be especially abundant in thymuses from patients with Myasthenia gravis (35).

According to these data, it has been proposed (35) that the primary antibody response in My-asthenia gravis might be directed against the AcChR component of an abnormal thymic epithelial cell which has become abnormal ("foreign") for unknown reasons (viral infection?). A mild epithelial cell hyperplasia might be one response to an exogenous agent while greater growth could result in thymoma both associated with various degrees of local lymphocyte response and production of an IgG anti-AcChR antibody which can result in clinical Myasthenia.

Along the same lines, other authors (34) have tried to take into account the fourth main characteristic of the disease (genetic linkage of the disease susceptibility to the major histocompatibility gene complex). According to them, there is a two-step pathogenetic mechanism under genetic control, at least one of the control loci being associated with the major histocompatibility gene complex. In the first step, pathological inductive stimuli, still unknown, cause intrathymic primitive stem-cells to differentiate to myogenic cells. In the second step, immunocompetent thymic lymphocytes react against these ectopic cells. The clinical stage is reached when autosensitized effector T lymphocytes leave the thymus and either infiltrate the synaptic space or participate in the formation of autoantibodies causing directly or indirectly the neuromuscular symptoms.

Thus, the major steps of the pathogenesis of Myasthenia gravis seem to have been elucidated. Although several important questions remain unsolved, one has now given a rational basis for using immunosuppressive agents. In addition, one has at disposal an extremely specific diagnosis test: anti-AcChR antibodies are present in the serum of more than 90 % of myasthenic patients and have never been formed in any other condition (36, 37).

In the future, most of the efforts will probably be devoted to the elucidation of the primary event in order to understand the origin of the disease, and to the development of methods to prevent it.

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