Pathophysiology of neuromuscular junction

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Scope

- Autoimmunity mechanism
- Normal neuromuscular transmission process
- Effect of antibody on neuromuscular transmission process
Myasthenia gravis (MG)

- A condition where voluntary muscles become easily fatigued (tired) and weak (especially muscle that work all the times; 6 muscles that move eye ball and muscle that hold the eye lid).
- A fault in the way nerve messages are passed from the nerves to the muscles.
- Due to a problem with the immune system (acquired immunological disorder and genetic abnormalities).
Myasthenia gravis (MG)

• The prevalence of MG in the US ranges from 0.5-14.2 per 100,000 people. The prevalence has increased over the past 2 decades.

• Female has more early onset (~30 years), than male (~50 years).
How immune system creates autoantibody?

- Toxic B-cell which could harm body’s own tissue escape the detection and destruction during fetal development. (McCalester University)
How immune system creates autoantibody?

Origin of Viral Onset Autoimmune Response

Unfortunately, the herpes simplex virus has the same peptide sequence in one area as the Ach receptor.

T-cells and B-cells attack and destroy a virus. In this case, herpes simplex.

T-cells and B-cells now mistake the Ach receptor as the herpes simplex virus. The body then begins an autoimmune attack on its own Ach receptors.

Infection can trigger.
How immune system creates autoantibody?

**Adult-Onset Autoimmune Response**

- Abnormal myoid cells in thymus.
  - Abnormal myoid cells of the thymus with Ach receptors.
  - These cells have mistaken Ach receptors as part of the foreign entity. Ach receptors are now recognized as foreign.
  - The body launches an autoimmune response on its own healthy Ach receptors.
  - T-cells and B-cells recognize abnormal myoid cell as defective or foreign and destroy it.
How immune system creates autoantibody?

Involve MHC class II
Myasthenia gravis is caused by a problem at the junction between the nerve endings and the muscle fibres.

- A nerve ending
- Acetylcholine is released from nerve ending
- Antibody
- Neuromuscular junction (gap between nerve and muscle)
- Receptor on surface of muscle fibre

Some receptors are stimulated by acetylcholine. Some receptors are blocked or damaged by antibodies.
Normal Neuromuscular Junction Structure
Normal neuromuscular junctions

Esterase stain
**Heteromeric Muscle AChRs**

Subunits: $\alpha 1$, $\beta 1$, $\gamma$, $\delta$, $\varepsilon$

Fetal Form:

Adult Form:

**Homomeric Neuronal AChRs**

Subunits: $\alpha 7$-$\alpha 10$

Major Subtype with High Affinity for Nicotine

Major Ganglion Subtype

**Heteromeric Neuronal AChRs**

Subunits: $\alpha 2$-$\alpha 6$, $\beta 2$-$\beta 4$

Likely Variants:

$\alpha 3$-$\beta 4$

$\alpha 4$-$\beta 2$

$\alpha 5$-$\beta 2$

$\alpha 3$-$\alpha 5$

$\alpha 4$-$\alpha 5$

$\alpha 3$-$\alpha 4$
• a gated receptor channel and intrinsic membrane glycoprotein of molecular weight 290,000, =
Antigen-presenting cells internalize the antigen (acetylcholine receptor), process it, and then present the processed peptides in association with major histocompatibility complex (MHC) class II molecules unique to the subject. The T-cell receptor of antigen-specific helper T cells (CD4+) binds to the specific MHC-peptide complex. The interaction of the antigen-presenting cell and the T cell requires additional costimulatory signals and is aided by adhesion molecules and cytokines, resulting in T-cell stimulation. The activated T cell helps acetylcholine-receptor-specific B cells. These B cells bind the antigen (acetylcholine receptor) to their surface antibodies, process it, and present the MHC-peptide complex, like other antigen-presenting cells. They thus interact with T cells by binding to the T-cell receptor. The T cell provides help to the B cells by means of surface molecules and cytokines (not shown), resulting in B-cell proliferation and the secretion of acetylcholine-receptor-specific antibody.
Modulation of post-synaptic AChRs by anti-AChR antibodies

Anti-AChR antibodies cross-link post-synaptic AChRs

Less efficient neuromuscular transmission

Anti-AChR antibodies cross-link post-synaptic AChRs

Internalized AChRs are degraded

Fewer AChRs remain on the post-synaptic membrane
Damage to Post-synaptic Membrane

Complement binds to the Antibody-AChR complex

Membrane-attack complex (MAC) forms on the membrane

The post-junctional membrane is damaged.
- Fewer post-synaptic membrane folds
- Reduced numbers of AChRs
- Widened synaptic cleft

Less efficient neuromuscular transmission
Antibody Mediated Mechanism: Blockade of Ach

Myasthenic Synapse

Ach has difficulty binding due to IgG blockage of the binding site. Ach rarely binds and Ach-esterase begins to break it down.

Normal Synapse

Ach has no difficulty binding and is broken down after binding has already occurred.
NEUROMUSCULAR JUNCTION ANATOMY: NORMAL & MYASTHENIA GRAVIS
The increased distance in the myasthenic receptor drastically cuts down on the chances of Ach finding one of the already scarce receptors. The Ach-esterase then "recycles" the Ach by breaking it into its component parts, acetate and choline.
Summary

Immune disorder

Nicotinic receptor

Decrease efficiency of neuromuscular transmission

Musk

Decrease efficiency of muscle contraction

Muscle weakness
Thank you very much for your attention