Nature and Action of Antibodies in Myasthenia Gravis

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KEYWORDS

• Acetylcholine esterases • Acetylcholine receptors • Autoantibodies • Complement • Muscle specific kinase • Neuromuscular transmission • Sodium channels

KEY POINTS

- This article discusses the antibodies associated with immune-mediated myasthenia gravis and the pathologic action of these antibodies at the neuromuscular junctions of skeletal muscle.
- We explain how the pathologic antibodies act, and consider the physiology of neuromuscular transmission with emphasis on 4 features.
- We describe the structure of the neuromuscular junction and the roles of postsynaptic acetylcholine receptors and voltage-gated Na^+ channels.
- We discuss the safety factor for neuromuscular transmission and how the safety factor is reduced in different forms of autoimmune myasthenia gravis.

ACETYLCHOLINE IS THE TRANSMITTER AT THE NEUROMUSCULAR JUNCTION

Acetylcholine (ACh) is stored in vesicles in the nerve terminal (**Fig. 1**).[1] ACh-containing vesicles are aligned near the ACh release sites or active zones where the vesicles will fuse with the presynaptic nerve terminal membrane.[1] Release sites are located opposite the clefts and between the tops of the secondary synaptic folds of the postsynaptic muscle membrane.[1–3] Transmitter release requires Ca^{2+} entry via P/Q-type Ca^{2+} channels.[4]

THE ROLE OF THE SYNAPTIC CLEFT

The space between the nerve terminal and the postsynaptic membrane, the synaptic cleft, is about 50 nm (see **Fig. 1**).[1] ACh diffuses across the synaptic cleft to activate

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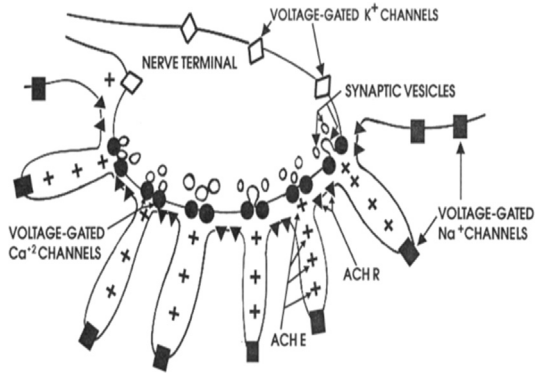

Fig. 1. Depiction of the neuromuscular junction. The nerve terminal is located above the secondary synaptic folds of the postsynaptic muscle membrane. The nerve terminal contains mitochondria, which produce the energy needed to synthesize acetylcholine (ACh) and package the ACh into synaptic vesicles. Synaptic vesicles can fuse with the nerve terminal membrane after an AP enters the nerve terminal. The nerve terminal contains voltage-gated K^+ channels (◇) and Ca^{2+} channels (●). Active zones, where Ca^{2+} channels are concentrated and synaptic vesicles fuse with the presynaptic membrane, are precisely aligned above troughs between secondary synaptic folds of the postsynaptic membrane. Within the synaptic cleft, the extracellular matrix contains acetylcholine esterase (AChE) (+) that is bound to the basal lamina of the postsynaptic membrane. The secondary synaptic folds contain a high density of acetylcholine receptors (AChR) (▼) on the tops of the secondary folds close to the nerve terminal membrane and a high density of Na^+ channels at the bottom of the troughs of the secondary synaptic folds (■).

ACh receptors (AChRs). Each synaptic vesicle releases about 10,000 ACh molecules into the synaptic cleft.[5] Adenosine triphosphate is also released from synaptic vesicles and the released adenosine triphosphate may modulate transmitter release of postsynaptic transmitter sensitivity.[6] An action potential (AP) in the nerve terminal stimulates between 50 and 300 synaptic vesicles to fuse (ie, the normal quantal content is between 50 and 300).[7] The diffusion of ACh across the synaptic cleft is very rapid owing to the small distance to be traversed and the high diffusion constant for ACh.[8] ACh esterase (AChE) in the basal lamina of the postsynaptic membrane and the synaptic cleft accelerates the disappearance of ACh from the synaptic cleft, as does diffusion of ACh out of the cleft.[9,10] Inactivation of AChE prolongs the duration of action of ACh on the postsynaptic membrane and slow the decay of the ACh-induced endplate current (EPC).[9] The concentration of AChE is approximately 3000 molecules/μm^2 of postsynaptic membrane.[9] AChRs have a concentration of about 15,000 to 20,000 molecules/μm^2 of postsynaptic membrane.[11] The concentration of AChE is great enough that most of the ACh entering a synaptic cleft is hydrolyzed to prevent AChRs from being activated more than once by nerve terminal released ACh.[12]

POSTSYNAPTIC MEMBRANE

The postsynaptic membrane is a complex collection of proteins that serve many purposes including the concentration and localization of 2 key elements, AChRs and voltage-gated skeletal muscle Na^+ channels, which convert the chemical signal from the motor neuron and ACh, into an electrical signal, the AP, that rapidly travels to the tendon ends of each muscle fiber. The AP triggers release of Ca^{2+} from