Practical Anatomy of the Neuromuscular Junction in Health and Disease

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KEYWORDS

• Neuromuscular junction • Motor neuron • Muscle • Active zone
• Acetylcholine receptors • MuSK • Voltage-gated calcium channels

KEY POINTS

- Neuromuscular junctions are excitatory chemical synapses that use acetylcholine as the neurotransmitter.
- Neuromuscular junctions form between nerve terminals of spinal cord motor neurons and skeletal muscles and are covered by perisynaptic Schwann cells and kranocytes.
- MuSK is indispensable for the accumulation of acetylcholine receptors at end plates.

NEUROMUSCULAR JUNCTIONS AND MOTOR NERVES

Neuromuscular junctions (NMJs) are excitatory chemical synapses formed between nerve terminals of spinal cord motor neurons and skeletal muscle fibers that use acetylcholine as the neurotransmitter. Muscle fibers in the skeletal muscles receive monosynaptic input directly from the lower motor neurons in the spinal cord (**Fig. 1**A). Therefore, motor neuron axons originating from the spinal cord travel a long distance to innervate muscle fibers. In most skeletal muscles, one muscle fiber has one NMJ. A mature NMJ is innervated by one motor nerve terminal (**Fig. 2**, *normal*); therefore, there is a one-to-one relationship between a given muscle fiber and motor neuron. However, one motor neuron innervates multiple muscle fibers by branching its axon within the innervation target muscle. This group of muscle fibers

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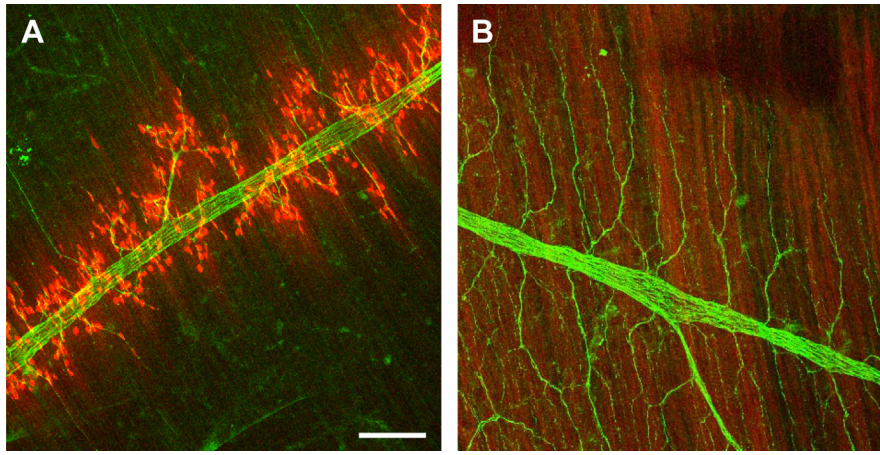

Fig. 1. Aberrant structures of presynaptic and postsynaptic differentiation in the diaphragm muscle from a MuSK$^{-/-}$ mutant mouse. A whole-mount diaphragm muscle from a wild-type (*A*) or a MuSK$^{-/-}$ mutant (*B*) was simultaneously stained with antibodies against neurofilament to label motor axons (*green*) and with rhodamine-labeled α-bungarotoxin to label acetylcholine receptors (*red*) on the postsynaptic muscle membrane. NMJs are not formed in MuSK$^{-/-}$ mutant mouse. Scale bar, 200 μm. (*From* Shigemoto K, Kubo S, Mori S, et al. The immunopathogenesis of experimental autoimmune myasthenia gravis induced by autoantibodies against muscle-specific kinase. In: Christadoss P, editor. Myasthenia gravis disease mechanisms and immune intervention. [Chapter 17]. New York: Linus Publication, Inc; 2009. p. 317; with permission.)

innervated by one motor neuron is called a motor unit. A nerve terminal innervates one NMJ and does not extend beyond the NMJ to innervate another muscle fiber (see **Fig. 2**, *normal*). This type of innervation differs from synapses of the central nervous system where axons can make *en passant* synapses or boutons *en passant* to form multiple synapses by one branch on an axon.

In the human diaphragm, two phrenic nerve bundles reach the center area of the right and left hemi-diaphragm. Each nerve bundle trifurcates and further splits in a radial fashion in the hemi-diaphragm, forming a net of nerve branches covering the muscle.[1] NMJs are often located in the center area of the muscle fibers and are arranged in a line among the nearby muscle fibers. The postsynaptic specialization of NMJs is often called the "end plate," also known as motor point, and the narrow distribution pattern of NMJs in a muscle is referred to as the "end plate band" (see **Fig. 1**A).

END PLATES AND ACETYLCHOLINE RECEPTORS

NMJs form in an indented area or a trough on the muscle cell membrane known as the synaptic gutter (primary gutter). These synaptic gutters are shown as a trough in scanning electron micrographs and an NMJ profile in transmission electron micrographs (**Fig. 3**, *control*). The postsynaptic muscle plasma membrane further invaginates to form the junctional folds (see **Fig. 3**B, *arrowhead*). These junctional folds extend from the postsynaptic membrane perpendicularly into the muscle cytosol. These junctional folds contribute to the increase in the muscle surface area to hold more acetylcholine receptors (AChRs) at the top of the junctional folds and part way down on the sides[2]; and the concentration of voltage-gated sodium channels at the trough of the