15 Innervation of Muscle and Neuromuscular Transmission

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15.1 Introduction

In contrast to the spontaneous activity displayed by smooth and heart muscle cells, striated muscle fibers of the skeletal muscle are directly controlled by central neuronal activity. Motor nerves contact muscle fibers at large chemical synapses called neuromuscular junctions or motor end plates (Fig. 15.1). The motor end plate where the nerve is connected to skeletal muscle represents the prototype of a chemical synapse in mammals. Here, each fiber of a skeletal muscle is connected to one particular motor neuron localized in the ventral horn of the spinal cord, while any given motor neuron innervates several muscle fibers. The motor neuron, together with all the muscle fibers with which it forms these synapses, is called a motor unit (see also Chaps. 45, 46, 49). The excitatory event of a motor neuron is transmitted along myelinated axons to the presynapses, where release of the synaptic transmitter acetylcholine (ACh) is induced. By opening ACh receptor channels, this release elicits a postsynaptic depolarization, which causes an action potential by opening sodium channels which depolarize the whole membrane area of the skeletal muscle fiber. The time between excitation of a motor neuron and the complete depolarization of the muscle fibers controlled by this neuron is short (1–10 ms). This is remarkable, since the distance between the motor neuron and the muscle fiber may be more than 1 m, the size of a muscle fiber may be up to 0.5 m, and the membrane area to be depolarized may be up to 1 cm². As a consequence, the speed of synaptic transmission and the synaptic efficacy of the neuromuscular end plate must be extremely high to allow a sufficient performance of motor control.

A great deal of pioneering research was performed on the neuromuscular junction, and it is the origin of several branches of modern biology, including the following:

- Patch-clamp and single-channel recording of ion channels
- Structure–function analysis and heterologous expression of ion channels
- Two-dimensional crystallization and ultrastructure analysis of membrane proteins
- Development-dependent expression and gene regulation of ion channels
- Analysis of protein determinants of synaptic structure
- Analysis of the processes underlying exocytosis and quantal transmitter release

Most of these subjects have since advanced far beyond the motor end plate and have extended to other fields of molecular research.

Of all the mammalian synapses the motor end plate has been most extensively studied, and the first pathophysiological concepts for the disturbance of synaptic transmission have been discovered. These are myasthenia gravis and the Lambert–Eaton syndrome.

In this chapter we have tried to present different views of the motor end plate, ranging from physiological function to development and structure to the molecular basis of end plate function and its pathophysiological aspects.


Motor neuron in the ventral horn of the spinal cord.

Motor endplate.

**Fig. 15.1A, B.** The motor end plate. A Location of the motor neuron in the ventral horn of the spinal cord. One motor neuron innervates several muscle fibers. B Structure of a motor end plate with junctional folds. Presynapse contains synaptic vesicles and Ca²⁺ channels. Postsynapse has nicotinic acetylcholine receptors (nAChR) and Na⁺ channels. The basal lamina is located in the synaptic cleft.

### 15.2 Mechanisms of Release and Subsequent Removal of Transmitter from the Synaptic Cleft

**Active Zone.** It is still not completely understood how a presynapse releases transmitter and how the transmitter molecules are subsequently removed again from the synaptic cleft. In the neuromuscular end plate, the concentration of the transmitter ACh increases from almost zero to about 1 mM in less than 100 μs and decreases again within about 1 ms. This enormous speed can only be explained by high rates of enzymatic reactions and by extremely short diffusion distances involved in elementary steps of this process. Nevertheless, it is now generally assumed that synaptic transmitter release is a process which is rather similar to the much slower Ca²⁺-dependent process of exocytosis of hormone-containing membrane vesicles in endocrine or mast cells [1]. Similar to secretory cells, the presynaptic terminal of the motor end plate contains lipid vesicles each carrying about 2000–5000 ACh molecules. To release transmitter, these