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REVIEWS

Modern Concepts of Cholinergic Neurotransmission at the Motor Synapse

A. I. Malomouzh[a, c, *] and E. E. Nikolsky[a, b, c, †]

[a] *Kazan Institute of Biochemistry and Biophysics, FRC Kazan Scientific Center of the Russian Academy of Sciences, P.O. box 30, Kazan 420111, Russia*
[b] *Kazan State Medical University, Kazan, 420012 Russia*
[c] *Kazan Federal University, Kazan, 420008 Russia*
**e-mail: artur57@gmail.com*

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Abstract—Cholinergic synaptic contact between motor neuron and skeletal muscle fiber is perhaps one of the core objects for investigations of molecular mechanisms underlying the communication between neurons and innervated cells. In the studies conducted on this object in the past few decades, a large amount of experimental data was obtained that substantially complemented a traditional view on synaptic transmission. In particular, it was established that (i) acetylcholine is released from the nerve ending in both quantal and non-quantal ways; (ii) molecular mechanisms of the processes of the quantal acetylcholine release—spontaneous and evoked by electrical stimuli—have unique features and can be regulated independently; (iii) acetylcholine release from the nerve ending is accompanied by a release of a number of synaptically active molecules modulating the processes of secretion or reception of the main mediator; (iv) signal molecules affecting the process of cholinergic neurotransmission can be released not only from the nerve ending but also from glial cells and muscle fiber; (v) molecular mechanisms of the regulation of synaptic transmission are highly diverse and go beyond the alteration of the number of the released acetylcholine quanta. Thus, the neuromuscular junction shall be deemed currently as complicated and adaptive synapse characterized by a wide range of multi-loop intercellular signaling pathways between presynaptic motor neuron ending, muscle fiber, and glial cells ensuring a high safety factor of synaptic transmission and the possibility of its fine tuning.

Keywords: cholinergic synapse, quantal and non-quantal release of mediator, cotransmission, neuromodulators, synaptic plasticity

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INTRODUCTION

Regulation, integration and hierarchy of cells within a multicellular organism, including a human one, are realized due to humoral and nervous systems. The nervous system is the key link in perceiving of information from external and internal environments, analysis of this information, and initiation of a response (including a motor one) of the whole body to an incoming signal. The nervous system functions because neurons can generate and conduct electrical signals that are transmitted to adjacent innervated cells in the regions of specialized cell junctions (*synapses*). The vast majority of these junctions are so-called chemical synapses, that is, junctions, in which an electric signal causes a release of a chemical mediator (*neurotransmitter*) from the neuron ending. The neurotransmitter diffuses through a synaptic cleft and interacts with special receptor proteins at the postsynaptic membrane of the innervated cell. Further events at the postsynaptic membrane depend on the receptor nature: either an electric signal is generated or/and the signal cascade of reactions that changes metabolism of the innervated cell is triggered.

A process of a signal transmission from a neuron to another cell is often referred to as *neurotransmission* and characterized further by an "ergicity"; that is, we specify a chemical structure of a mediator responsible for the transmission of an electric signal. For example, in the case of synapses, whose neurotransmitter is acetylcholine, we speak of a *cholinergic* nature of the transmission.

A wide range of factors makes the study of cholinergic signal transmission a challenging issue. First, the cholinergic neurons are presented in a number of brain structures (including brainstem, mesencephalon, and cerebral cortex), and their axons innervate various zones of cortex and a number of subcortical zones. The cholinergic system plays a key role in the mechanisms of attention [1], memory, and learning [2]. Second, the cholinergic transmission is the main system

† Deceased.