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GENETICS

Dysfunction of Neuromuscular Synapses in the Genetic Model of Alzheimer's Disease

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The function of synaptic transmission and presynaptic vesicular cycle in the neuromuscular synapses of the diaphragm was studied in transgenic APP/PS1 mice (Alzheimer's disease model). The decrease in the quantal content of end-plate potential, intense depression of the amplitude of terminal plate potentials under conditions of lasting high frequency stimulation (50 Hz), a drastic prolongation of the synaptic vesicle recycling time in APP/PS1 mice in comparison with wild type mice were detected. Manifest dysfunction of the neuromuscular synapses, caused by disordered neurosecretion and recycling of the synaptic vesicles in the presynaptic nerve endings, was detected in the Alzheimer's disease model on transgenic APP/PS1 mice. The study supplemented the notions on the pathogenesis of Alzheimer's disease as a systemic disease, while the detected phenomena could just partially explain the development of motor disorders in this disease.

Key Words: *Alzheimer's disease; neuromuscular synapse; synaptic transmission; presynaptic vesicular cycle; neuromediator secretion*

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease and the main cause of dementia. Despite numerous studies aimed at creation of pharmacological and gene and cell approaches to its treatment, AD remains incurable. Excessive production and accumulation in the nervous and other tissues of neurotoxic β-amyloid peptide (β-AP) underlies the disease development; the cholinergic neurons are the first that suffer [2,7].

Disorders in the interneuronal synaptic transmission and plasticity serve the base for cognitive disorders and loss of memory in AD [7]. Synaptic dysfunction in the hippocampus and cerebral cortex in AD starts long before overall neuronal death, which suggests considering it as a synaptic abnormality [7,10].

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By the present time there are no data on the status of the neuromuscular synapses in AD. This problem is clinically significant, as patients with AD can exhibit motor disorders: tremor, bradykinesia, myoclonus, gait disorders, oculomotor disorders, *etc.* [3,9,12,13]. Some of these symptoms can be caused by the toxic effect of β-AP and other pathological factors on the neuromuscular system, which is proven by high level of β-AP in the patients' skeletal muscles [4]. Previously we have detected disorders in the skeletal muscle contractility and electrogenesis on AD models [1,2,5,6].

Now we study the function of synaptic transmission and presynaptic vesicular cycle in the neuromuscular synapses of transgenic mice with AD model.

MATERIALS AND METHODS

Experiments were carried out on the mouse diaphragm neuromuscular preparations. In order to prevent con-