INVESTIGATION OF THE ULTRASTRUCTURE OF NEUROMUSCULAR SYNAPSES IN THE LAMBERT – EATON MYASTHENIC SYNDROME

L. L. Babakova, E. A. Kolomenskaya, N. V. Ostrovskaya, and O. M. Pozdnyakov

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The ultrastructure of neuromuscular synapses of patients with the Lambert–Eaton myasthenic syndrome was investigated. An increased content of synaptic vesicles in the axon terminals and an increase in the number and depth of anastomosing synaptic folds were found in most synapses. Local destructive changes were detected in the terminals of some synapses. The observations confirm the view that this syndrome is based on a disturbance of the liberation of mediator from the presynaptic structures.

KEY WORDS: neuromuscular synapse; Lambert–Eaton myasthenic syndrome.

The view that the accumulation, storage, and liberation of synaptic mediators are connected with the synaptic vesicles (the quantum vesicular theory) is nowadays hardly in question. At the same time, it is rare to find correlation between the state of the vesicular system of axon terminals and the level of function of the neuromuscular synapse. This is evidently because the normal neuromuscular synapse has a high degree of reliability. Structural-functional correlations are more easily observed following deliberate injury to the mechanisms lying at the basis of synaptic transmission [3-6, 8, 13, 14].

This paper describes the results of an investigation of the ultrastructure of neuromuscular synapses in the myasthenic syndrome, a condition considered [1, 10-12] to be due to a disturbance of the liberation of mediator from the presynaptic structures.

EXPERIMENTAL METHOD

Pieces of muscles from the synaptic zone of the palmaris longus muscle, taken at diagnostic biopsy from two patients with the Lambert–Eaton myasthenic syndrome were investigated. The material was fixed successively in formol–sucrose and osmium tetroxide and embedded in Araldite. Sections were stained with uranyl acetate and lead citrate by Reynolds' method and examined in the IEM-7A electron microscope.

EXPERIMENTAL RESULTS

Electromyographic investigation of the patients revealed a synaptic defect characteristic of this disease.

On electron-microscopic investigation changes were found in the pre- and post-synaptic structures of the neuromuscular junctions. In most synapses the number of synaptic vesicles in the axon terminals was increased, sometimes considerably (Figs. 1-3). Practically the whole of their free volume in the axon terminals of some synapses was filled with vesicles. Their axoplasm was electron dense and granular.

Laboratory of Experimental Pathomorphology and Ultrastructural Characteristics of Pathological Processes, and Laboratory of Clinical Pathophysiology, Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR A. M. Chernukh.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 81, No. 1, pp. 79-80, January, 1976. Original article submitted April 18, 1975.

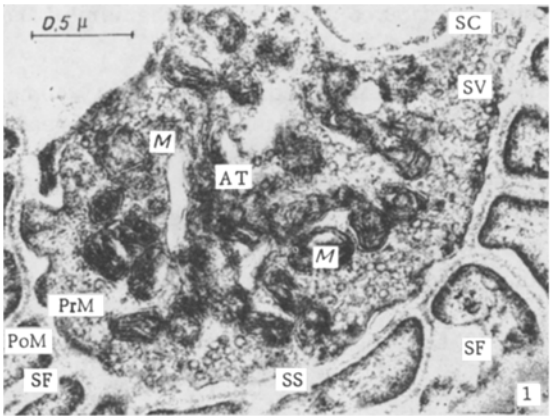

Fig. 1

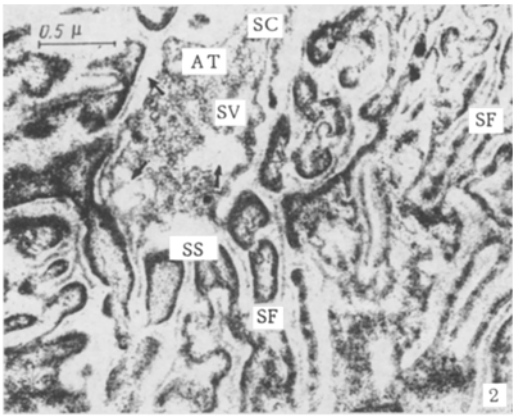

Fig. 2

Fig. 1. Neuromuscular synapse in Lambert–Eaton myasthenic syndrome: increased number of synaptic vesicles in an axon terminal (40,000×). Here and in Figs. 2 and 3: AT) axon terminal; SV) synaptic vesicles; M) axoplasmic mitochondria; SS) synaptic space; SF) synaptic folds; SC) processes of Schwann cells; PrM) presynaptic membrane; PoM) postsynaptic membrane.

Fig. 2. Neuromuscular synapse in Lambert–Eaton myasthenic syndrome: large number of synaptic vesicles in axon terminal in which areas of destruction are present (arrows); synaptic space variable in width and electron density; increased folding of postsynaptic membrane (30,000×).

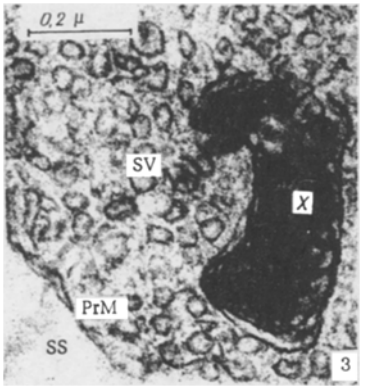

Fig. 3. Part of axon terminal of a neuromuscular synapse in Lambert–Eaton syndrome; X) structure containing electron-dense vesicles (100,000×).

The presynaptic membrane was irregularly stained, giving the impression of discontinuity. Because of the increased number of synaptic vesicles, hardly any neurofilaments could be detected. The axoplasmic mitochondria were normal in structure and their number was not increased on the average. Sometimes structures bounded by double membranes, containing electron-dense vesicular formations of the same size as synaptic vesicles, could be seen in the terminals (Fig. 3).

Degenerative changes were observed in some terminals and caused their partial destruction (Fig. 2) with a decrease in area of synaptic contact. The synaptic space in such synapses was variable in width and in the electron density of its contents.

Changes in the postsynaptic structures concerned chiefly the synaptic folds, the number and depth of which were considerably increased; the folds branched repeatedly and anastomosed with each other (Fig. 2). The substance of the synaptic folds usually had uniform electron density and a central band could be clearly distinguished in it.

The end-plate of the neuromuscular synapses as a rule was widened. Processes of Schwann cells, adjacent to the axon terminals, had increased electron density.

The most characteristic features of the neuromuscular synapses in Lambert–Eaton myasthenic syndrome are thus an accumulation of synaptic vesicles in the axon terminals and excessive folding of the postsynaptic membrane. The accumulation of synaptic vesicles in the terminals has been found during the action of large doses of tetanus toxin on the neuromuscular synapse, blocking the liberation of mediator as shown by electrophysiological investigations [3-5]. An increase in the number of synaptic vesicles also was observed when magnesium ions were added to the fixative; under these circumstances the process of neurosecretion is also known to be disturbed [7].

Electrophysiological investigations (including microelectrode studies) in Lambert–Eaton syndrome [1, 10-12] indicate a deficiency of acetylcholine mediator in the neuromuscular synapses, resulting from a

disturbance of its secretion. The results of the present investigation confirm this mechanism of the disturbance of synaptic function.

The increase in number and size of the synaptic folds can be interpreted as a secondary compensatory reaction of the postsynaptic membrane to chronic mediator insufficiency. An increase in the area occupied by synaptic folds and in their number was discovered in a histometric investigation of the neuromuscular synapses of patients with the Lambert–Eaton myasthenic syndrome [9]. However, no accumulation of synaptic vesicles in the terminals was found in that investigation. In the present writers' view, the reason for this could be differences in the method used to treat the tissue, for fixation has been shown to have a powerful effect on the process of mediator liberation in the neuromuscular synapse [2].

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