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論　文　概　要

The neuromuscular junctions (NMJs) in skeletal muscle fibers are functionally distinct compartments of the subsarcolemmal and extracellular matrix domains that contain variants of the sub- and trans-sarcolemmal components and of the extracellular matrix. The NMJ is the only synaptic link between a motor neuron and the muscle fiber it innervates. It is a chemical synapse that is anatomically and functionally differentiated for the transmission of signals from the motor nerve terminal to a circumscribed postsynaptic region on the muscle fiber. The NMJs of mammalian skeletal muscle have several components: (1) a Schwann cell process that forms a cap above the portion of the nerve terminal that does not face the postsynaptic region; (2) a nerve terminal, which contains the neurotransmitter acetylcholine; (3) a synaptic space lined with basement membrane; (4) a postsynaptic membrane containing acetylcholine receptors and acetylcholine esterase; and (5) junctional sarcoplasm, which provides structural and metabolic support for the postsynaptic region.

We evaluated the effects of brief, temporary denervation caused by ischiadic nerve-freezing on the processes of degeneration and regeneration of ultrastructural features in neuromuscular junction (NMJ) architecture in different types of rat skeletal muscle fibers. Nerve terminal (NT) area was decreased significantly 12 hours after nerve freezing in both fast-twitch (FT) and slow-twitch (ST) fibers. One day after nerve freezing, some terminal axons were absent; decrease in NT area was remarkable in ST fibers, and there was retraction of Schwann cells and perineural epithelial cells. Fiber type-specific differences were observed in pattern of decrease in NT area between 24 hours and 7 days after nerve freezing (there was significantly more decrease in FT fibers). The primary synaptic cleft became shallow, and the secondary junctional folds shorter and wider, but the basement lamina filling the subneural apparatus was unaltered. The number of secondary junctional folds decreased gradually between 6 hours and 14 days after nerve freezing in both types of fiber. In control muscle fibers, synaptic vesicle density (SVD) per terminal area was significantly higher in FT fibers. SVD densities decreased following nerve freezing-induced destruction of NMJs, and were minimal 3 days in FT fibers or 7 days ST fibers after nerve freezing. At 3 weeks, regeneration of both FT and ST fibers was well advanced, and all parameters had recovered to control values in FT fibers 28 days after nerve freezing. The effects of structural degeneration of NMJs were less pronounced in FT fibers, and regeneration tended to be earlier in FT than in ST fibers.

These findings indicate that maintenance of the cup-shaped primary folds is dependent upon neurotrophism, while secondary junctional fold structure is not. If muscular activity were the only trophic influence on skeletal muscle fibers, then denervation would affect NMJs in all fiber types to the same extent, and any difference in rate of degeneration between the two types of muscle fibers would be due to factors intrinsic to them. If, however, neurotrophic factors (postulated to be one component of the dense-core vesicles in the nerve terminals) are partially responsible for maintenance of muscle fiber structures, then differences in rates of degeneration and regeneration of NMJs in different types of muscle fibers could result in differential withdrawal of neurotrophic substances. Severe degradation of the ultrastructural features in NMJs occurred due to temporary denervation during muscle fiber degeneration

processes, and these structural changes were all reversible and fiber type-specific.

論 文 審 査 の 要 旨

学位論文の「Plasticity of neuromuscular junction architectures in rat slow and fast muscle fibers following temporary denervation and reinnervation processes」は、2006 年 11 月発行の J. Muscle Res. Cell Motil.の第 27 巻、8 号に原著論文として掲載された（607-615）。研究内容の主体は、骨格筋細胞における神経筋接合部の形態変化を機能的特性と関連させ、組織化学的手法により検討したものであり、最新のバイオイメージング技術を駆使して実施した極めて独創性の高い研究成果であった。骨格筋細胞のタイプ移行に関係する運動神経細胞の支配様式は、筋線維タイプ別に異なることが報告されているが、神経筋接合部の形態的特性も大きく異なることに加え、生理的・非生理的刺激に応答して比較的容易にその形態的特徴を変化させることによって機能的特性の変化を引き起こしていると推察された。

学位論文審査委員会では合議によって、本研究内容に加えて関連する研究成果を総合的に判断し、本論文は博士の学位を授与するに十分な研究成果を含む内容であると判定した。