passive transfer of MuSK antibodies from MG patients into animal hosts. However, the injection of a large amount of human MuSK antibodies into mice can barely induce EAMG (36). The mechanisms employed by these antibodies include multiple events during which MuSK functions stall in their process of regulating synapse formation and maintenance (37). MuSK antibodies against compound antigenic determinants in the extracellular domain may engage in their pathogenic activities through antigenic modulation and/or restraint of MuSK functions, and the consequences of these effects range from a partial to entire loss of MuSK function without the involvement of complement-mediated damage. The point that MuSK antibodies in MG patients are mainly of the IgG4 subclass, which does not activate complement, may be relevant here. These diverse possibilities reflect the complexity of clinical features seen in such patients ranging from typical MG throughout its many variants.

Aging and NMJs

How can we extend the studies of MG to understand *sarcopenia*? The structural changes of NMJs in aged rats have suggested that active remodeling mechanisms at the synapse between nerve and muscle may play crucial roles in the progression of *sarcopenia* (Figure 8) (38). Our studies of MG with MuSK antibodies demonstrated that the structure of NMJs is not statically maintained; rather, the nerve-to muscle and muscle-to nerve signals stimulate dynamic assembly and disassembly of NMJs' molecular complexes. A steady flow of molecular complexes at NMJs sustains both the structures and functions of the motor system including motoneurons and muscles. However, we do not completely understand the molecular mechanisms, although our animal models of MG demonstrated clearly that muscle-to-nerve signal transduction requires the maintenance of NMJs (37). We think that studying MG caused by the failure of NMJ maintenance will facilitate further progress in resolving the molecular basis of muscle atrophy. Additional areas of relevance are the many physical conditions, including aging, injury, cancer or AIDS, in which muscles shrink or atrophy. Understanding the molecular basis of NMJ maintenance promises to provide new targets for innovative therapeutics to create healthy, enduring muscles.

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Figure Legends

Figure 1. Structure and molecular architecture of the NMJ.
Drawings show progressive enlargement of segments of a NMJ. The presynaptic terminals consist of multiple swellings called synaptic terminals covered by a thin layer of Schwann cells. The nerve terminal occupies a shallow gutter in the muscle fiber and is capped by processes of Schwann cells. ACh from 150 to 200 vesicles is released from the active zones in the nerve terminal, which directly oppose junctional folds in the postsynaptic membrane. The terminals are separated from the postsynaptic cell by the synaptic cleft, which is about 50 nm wide. AChRs, MuSK and rapsyn concentrated at the peaks of postsynaptic folds are shown, with their subcellular localizations indicated by bars. Voltage gated sodium channels are localized in the depths of postsynaptic folds.

Figure 2. Schematic representation of the MuSK domain structure and expression of secretory MuSK proteins in COS-7 cells. The domain structures of recombinant secretory MuSK protein (MuSK-His and MuSK-Fc) and receptor-type MuSK are shown. The whole coding region of the MuSK extracellular domain was fused with the His-tag or Fc region of human IgG1 as shown.

Figure 3. Rabbits manifest myasthenia gravis (MG)-like paresis after immunization with MuSK protein.
(A) Two rabbits representative of four animals with positive outcomes developed myasthenic weakness after immunization with the recombinant MuSK protein. After three injections of MuSK protein, M1 and M2 rabbits manifested flaccid weakness within three and nine weeks, respectively. M2 rabbit developed severe exhaustion with muscle weakness. (B) Cross-sections from the soleus muscles of two paretic (M1 and M2) and a normal rabbits (Normal) were stained with H&E. Muscle fibers in M1 paretic rabbit showed only subtle changes in shape and size, whereas atrophy of muscles fibers in M2 paretic rabbit was observed as small angular fibers (indicated by arrows). Scale bar, 50mm. (C) Electromyograms recorded from M1 paretic rabbit. The retro-auricular branch of the facial nerve was continuously stimulated with constant square-wave pulses of 0.1 msec at 20 Hz delivered by a current stimulator, and the compound muscle action potential (CMAP, second peak observed on the oscilloscope

screen recorded at the indicated time-points during stimulation) showed a decremental pattern, consistent with MG.

Figure 4. Manifestations of MG after injection of purified MuSK proteins in a mouse.

Figure 5. Inhibition of agrin-induced and agrin-independent AChR clustering by MuSK antibodies. (A) C2C12 cells were treated with agrin, laminin-1, or VVA-B4. AChR clusters were stained with rhodamine-conjugated BTX. AChR clustering induced by agrin, laminin-1, and VVA-B4 was inhibited in the presence of MuSK antibodies. This inhibition was blocked by absorption of the MuSK antibodies with MuSK-AP before treatment of the cells. Scale bar: 20 mm. (B) Quantification of the inhibitory activity of the MuSK antibodies confirmed that they significantly inhibited agrin-, laminin-1–, and VVA-B4-induced AChR clustering. Preabsorption of the MuSK antibodies with MuSK-AP significantly blocked inhibition. Values represent means ± SEM of 10-15 fields for each of the 2 experiments per treatment. *$P < 0.01$ versus similar treatment without MuSK antibodies; #$P < 0.01$ versus similar treatment without preabsorption; ANOVA. J. Clin. Invest. 2006; 116:1016-1024. Copyright 2009 The American Society for Clinical Investigation.

Figure 6. Reduction of the size and density of AChR clusters at the NMJs in paretic rabbits. (A) Cross sections from the soleus muscles of 2 paretic (M1 and M2) and 3 normal rabbits (N1, N2, and N3) were stained with 10 nM rhodamine-conjugated BTX. Bright crescents of bound BTX, indicative of endplate AChR, were smaller and less intense in the paretic rabbits' muscle fibers than in those of the normal rabbits. Arrows indicate the small angular fibers in M2 soleus muscles. L, left; R, right. Scale bar: 50 mm. (B) Images of 10 AChR clusters at NMJs in the right and 10 in the left soleus muscles of the paretic and normal rabbits were randomly recorded by a digital imaging camera. Quantification of the area and intensity of AChR clustering in the unprocessed images were measured using NIH Image software. Bars indicate means ± SD. *$P < 0.01$ versus normal rabbits. J. Clin. Invest. 2006; 116:1016-24. Copyright 2009 The American Society for Clinical Investigation.

Figure 7. Schematic appearance of NMJs observed in normal humans and MG patients.

(A) Normal NMJ. AChRs are concentrated at the peaks of abundant and well-preserved, highly complex convoluted junctional folds. (B) and (C) NMJs observed in experimental animals that model MG induced by MuSK antibodies and in patients with the congenital myasthenic syndrome from MuSK or Dok-7 mutations. Small NMJs in both pre- and post-synaptic structures. (B) Attenuation of AChR and reduced complexity of synaptic folds at post-synaptic membranes without widened synaptic spaces. (C) Disappearance of post-synaptic folds with preserved synaptic space. (D) NMJs in MG patients with AChR antibodies. The myasthenic junction has a reduced number of AChRs, simplified synaptic folds and a widened synaptic space with a normal nerve terminal.

Figure 8. Scanning electron micrographs of NMJs in extensor digitorium longus muscles of young and aged subjects. (A) In a 4-month-old rat. Convoluted and winding synaptic gutters with numerous slit-like junctional folds. (B) In a 22-month-old rat. A number of cup-like depressions with slit-like junctional folds link together. A nerve ending, which faces toward the muscle apparatus, consists of numerous small protrusions of the terminal axons that may represent individual depressions. X3000 (scale bar 5 mm). Reprinted from Desaki et al. Virchows Arch. 2000;437:388-95.

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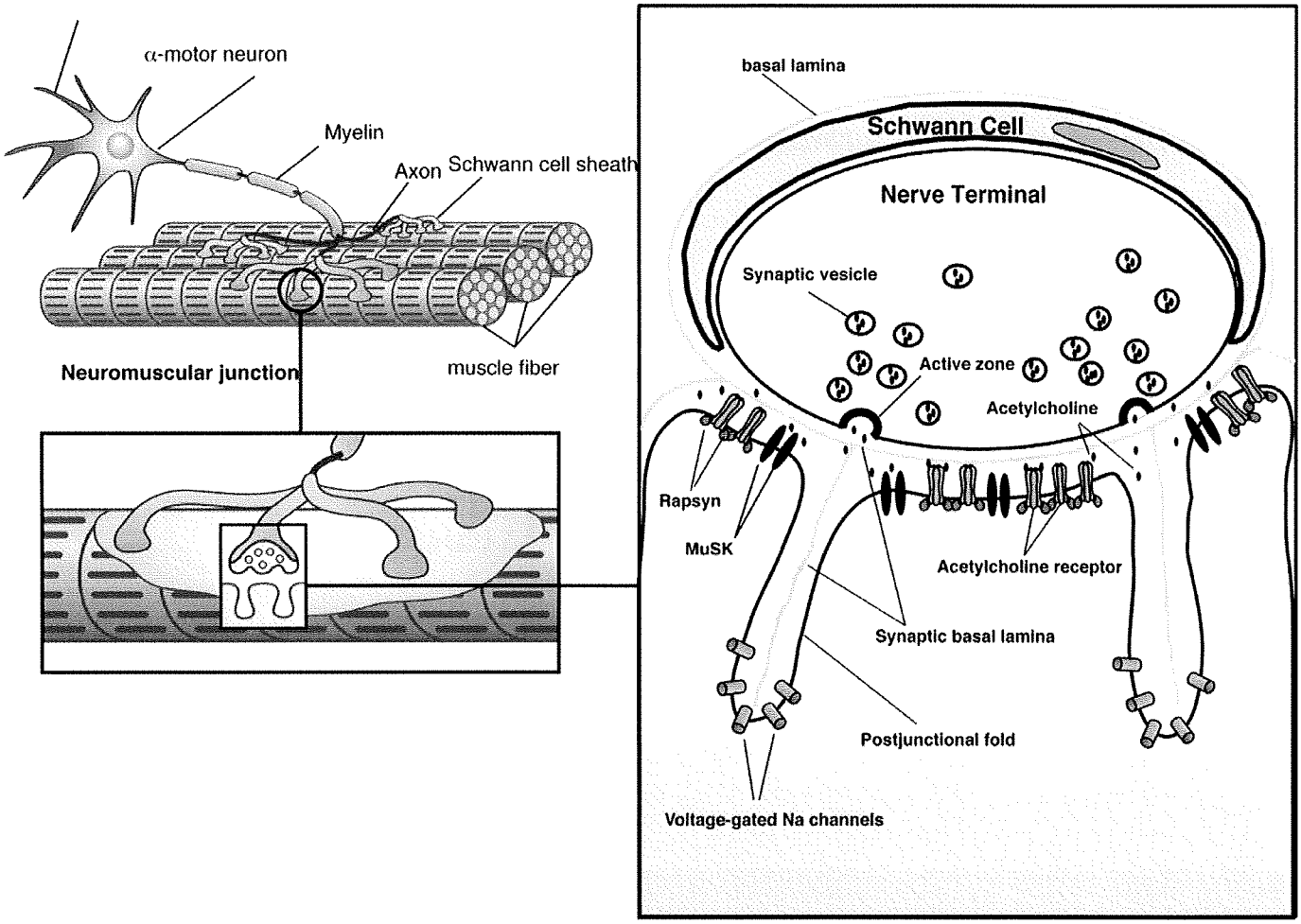
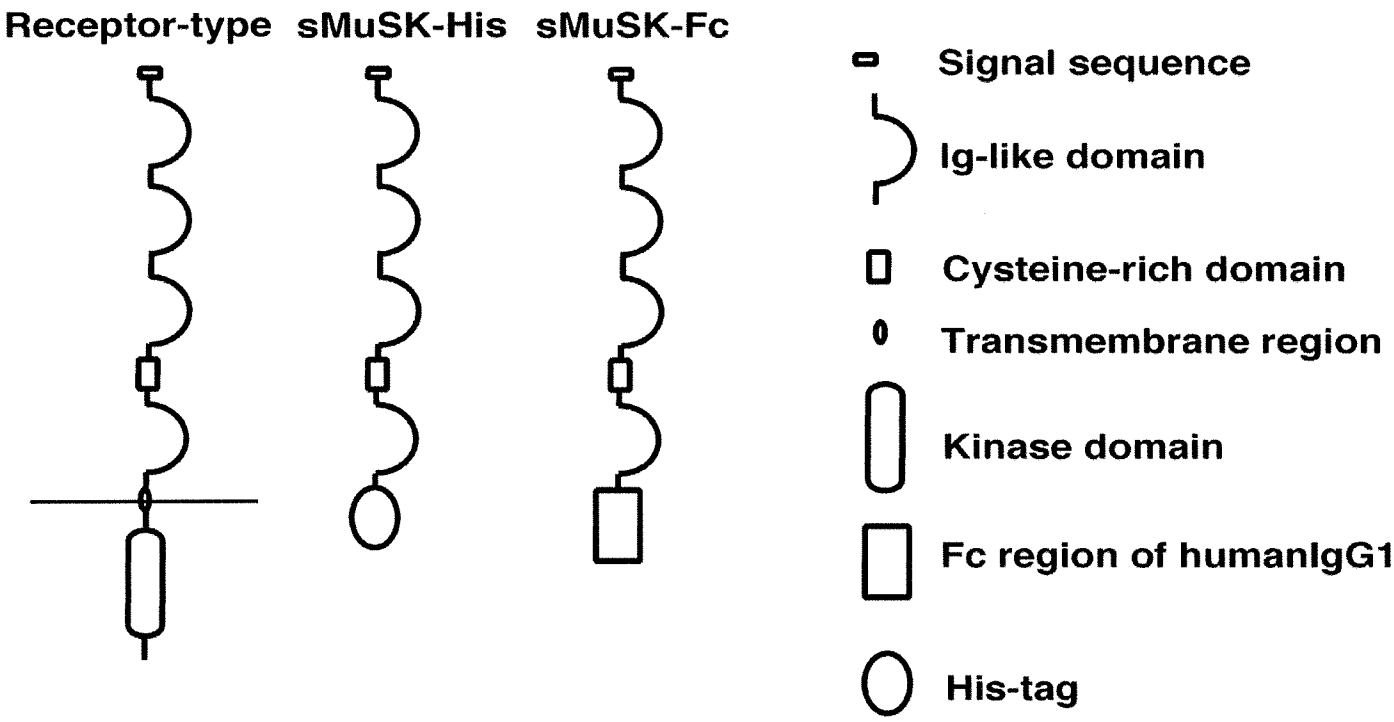

α-motor neuron
Myelin
Axon
Schwann cell sheath
Neuromuscular junction
muscle fiber
basal lamina
Schwann Cell
Nerve Terminal
Synaptic vesicle
Active zone
Acetylcholine
Rapsyn
MuSK
Acetylcholine receptor
Synaptic basal lamina
Postjunctional fold
Voltage-gated Na channels


Receptor-type
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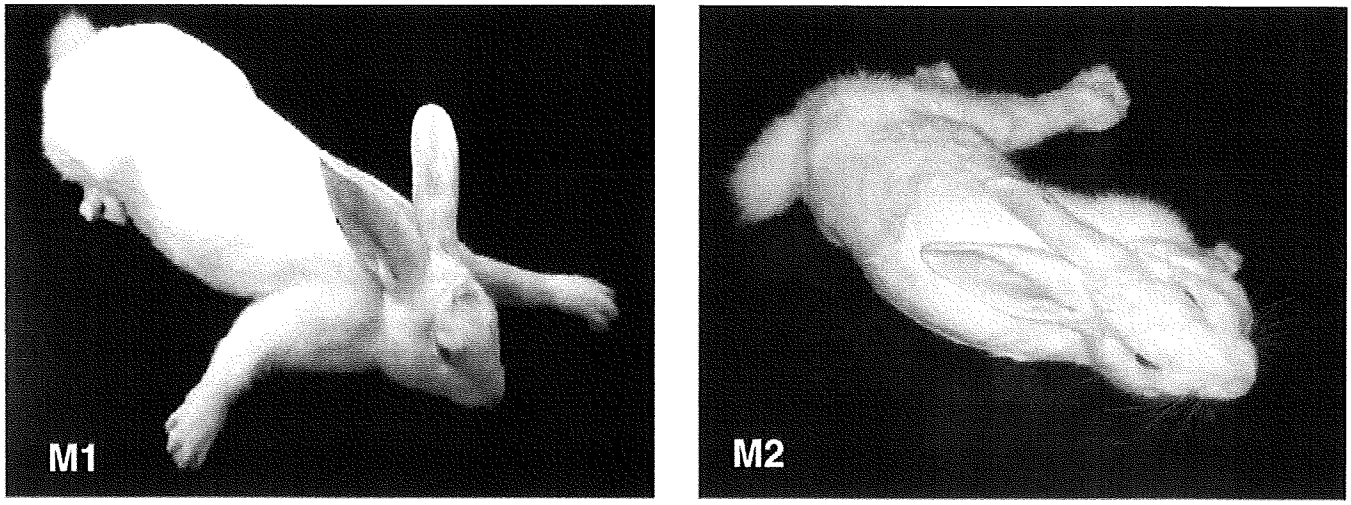
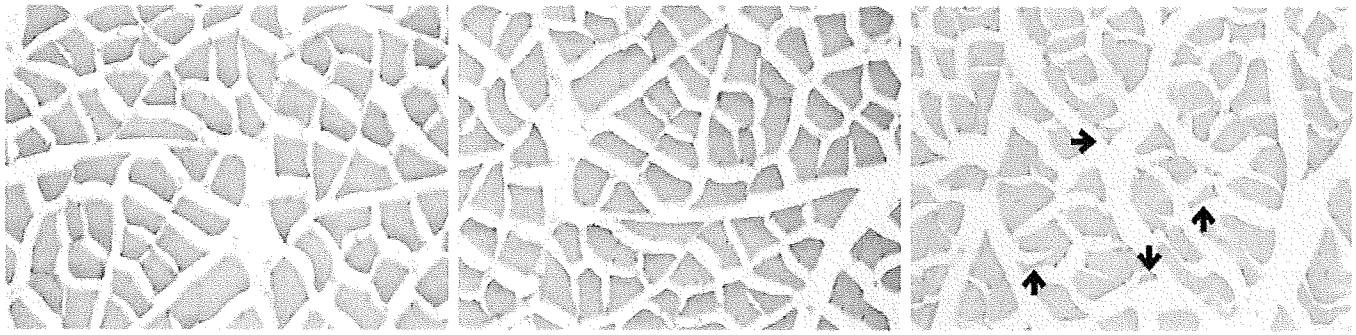
His-tag

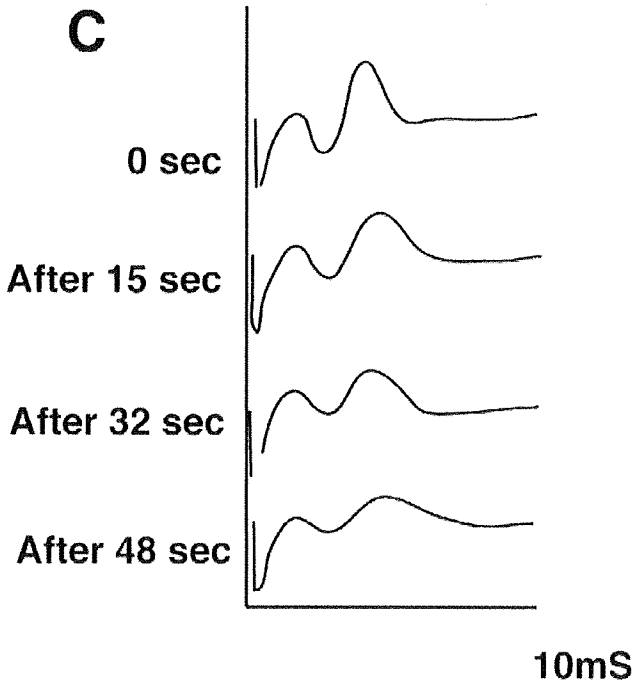
A


M1
M2

B


Normal
M1
M2

C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After 15 sec
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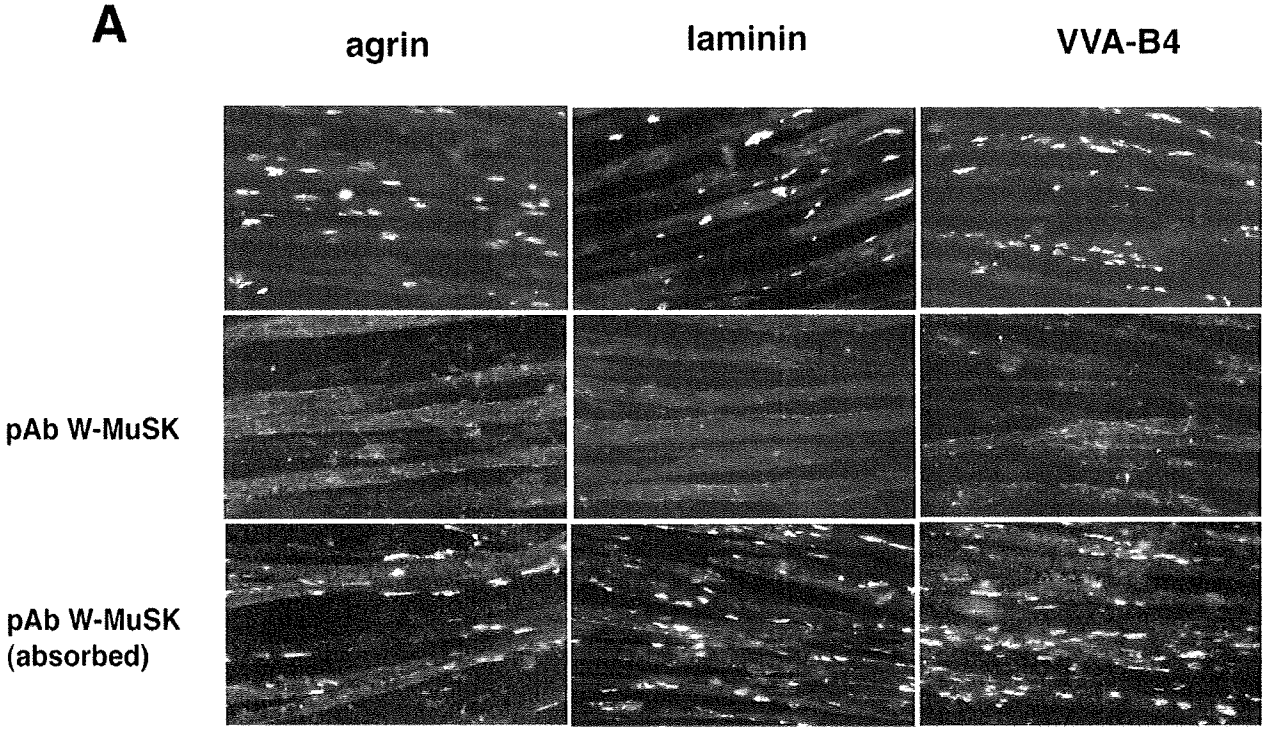
10mS

A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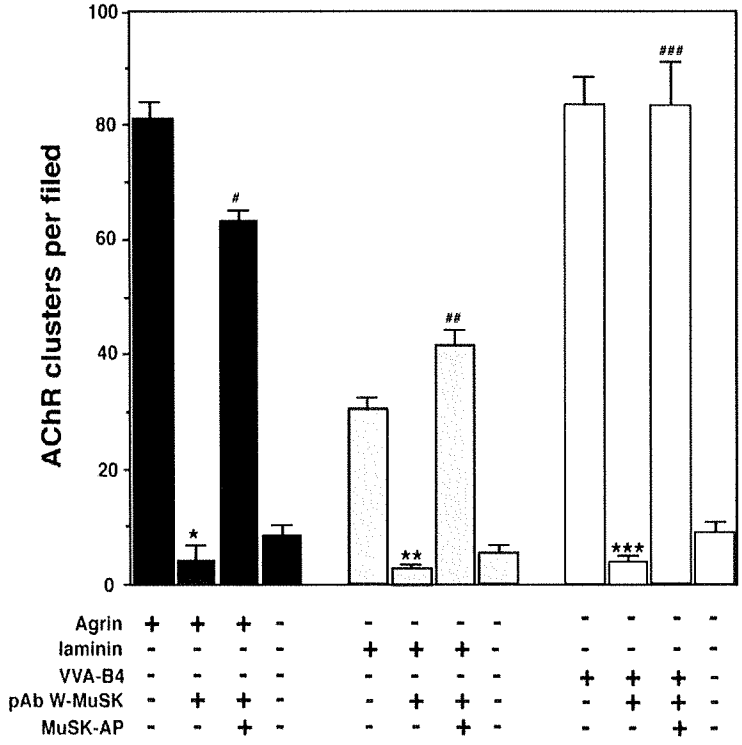
laminin
VVA-B4
pAb W-MuSK
pAb W-MuSK
(absorbed)

B


AChR clusters per filed
100
80
60
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Agrin + + + - - - - - - - - -
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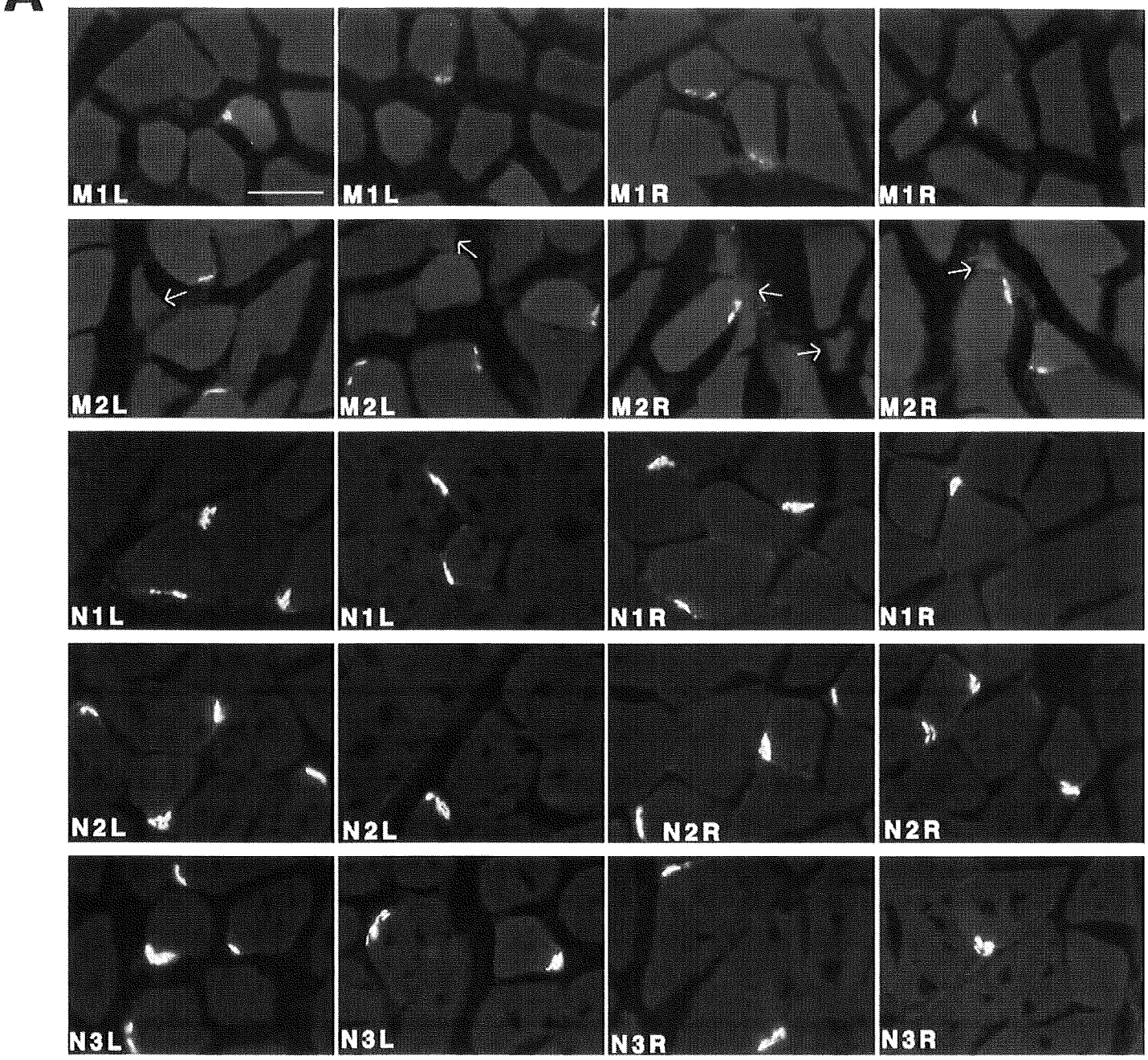
A
M1L
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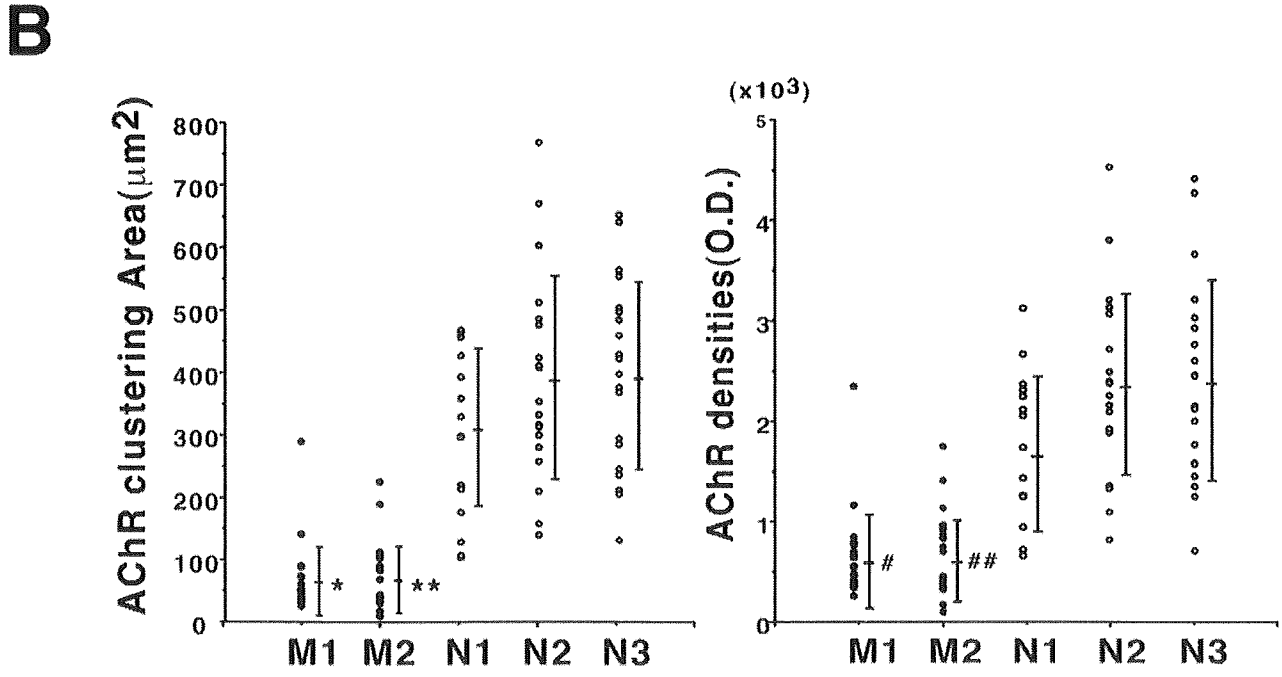
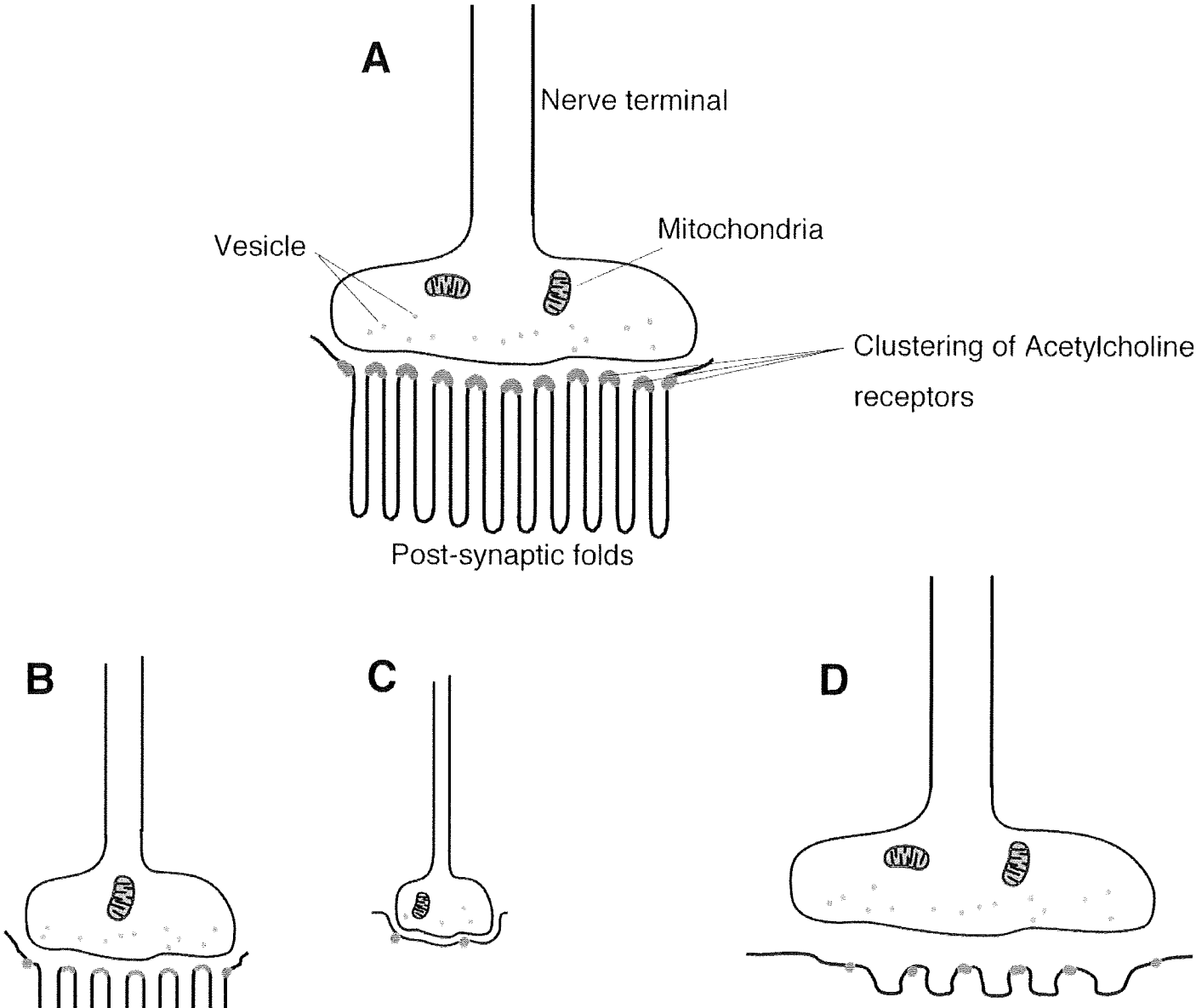

B
AChR clustering Area(μm2)
800
700
600
500
400
300
200
100
0
*
**
M1
M2
N1
N2
N3
(x10³)
AChR densities(O.D.)
5
4
3
2
1
0
#
##
M1
M2
N1
N2
N3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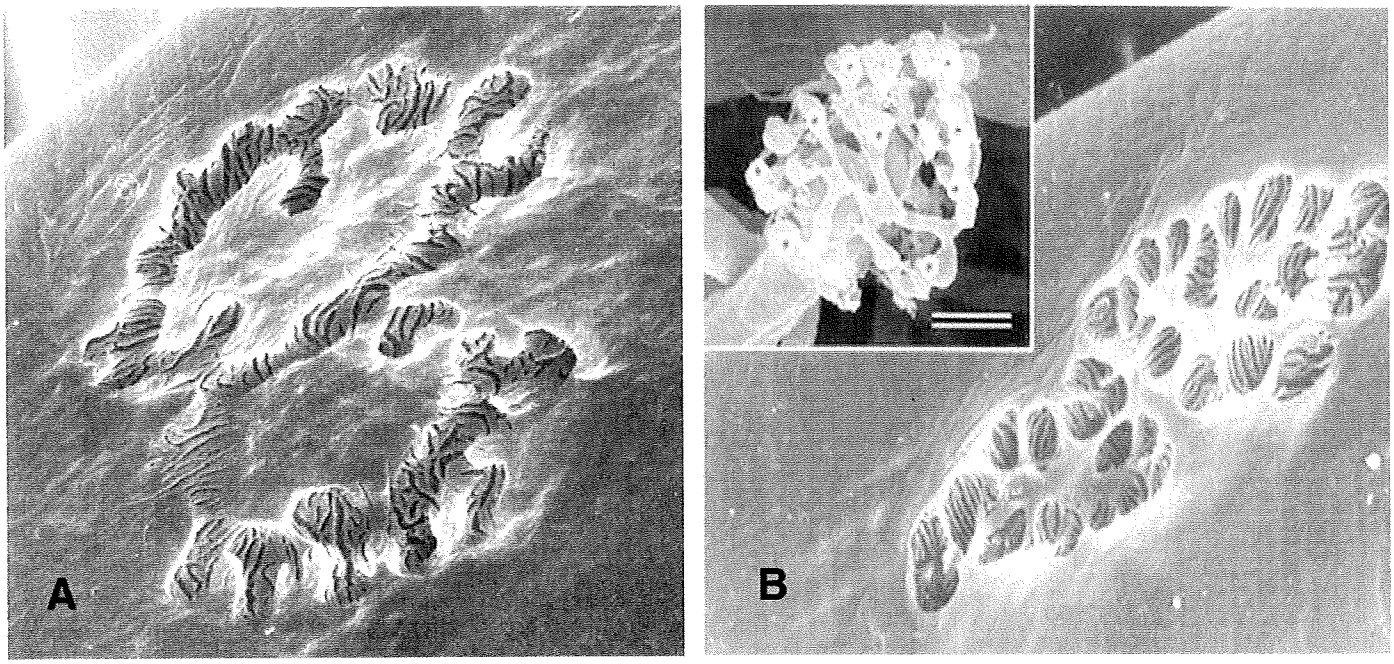
Vesicle
Clustering of Acetylcholine receptors
Post-synaptic folds
B
C
D
MuSK antibodies
AChR antibodies


A
B

老年医学の展望

神経筋接合部位の異常と筋力低下

重本　和宏　　久保　幸穂　　丸山　直記

要　約　サルコペニア（加齢性筋肉減少症）は転倒によるけがの危険性を増加させ，場合によってはそれによって身体的自立を妨げ，また障害を引き起こし身体活動量の低下を招く．さらに，サルコペニアによる運動機能低下-寝たきり-認知症の悪循環は，重度心身障害者の要介護増加に繋がっていく．従って，老化によって筋萎縮に至るメカニズムの解明は，その科学的根拠に基づいた早期予防，リハビリの有効性および効果判定，新しい運動処方の開発の基盤として必須である．最近，筋は運動神経の支配下にあって一方的に維持されるのではなく，筋が中枢側の運動神経を維持する機構が存在することがわかってきた．つまり，筋と運動神経は適切な運動習慣によって保持される動的な相互作用で互いを維持していることになる．この機構の重要性は，神経筋接合部の筋側に発現するMuSK（muscle-specific kinase）に対する自己抗体で発症する重症筋無力症の病態研究から明らかとなった．重症筋無力症は高齢社会を背景に18年前の全国調査と比較して2.5倍に患者数が増加しているが，我々は重症筋無力症がアセチルコリン受容体(AChR)だけでなく，MuSKに対する自己抗体で発症することを世界で初めて示した．筋と運動神経の間の維持機構を明らかにすることができれば，筋萎縮の原因解明と治療法の開発に大きな進歩をもたらすと予想される．

Key words：neuromuscular junction，muscle-specific kinase，myasthenia gravis，muscle weakness，sarcopenia

（日老医誌　2009；46：106-113）

はじめに

サルコペニアは認知症と並んで介護予防の面から社会的要請の強い重要な研究課題である．一方で，筋萎縮をもたらすサルコペニアは筋・運動神経の機能維持システムを解明するための手がかりとなる重要な生物学的表現形の一つである．筋萎縮の原因解明と予防・治療法の開発には，生命現象の普遍的原理の探求として設定した目標に向けて研究を推進する必要があると考えている．我々のグループは新しい視点から老化研究に取り組んでいる．サルコペニア（加齢性筋肉減少症），廃用性筋萎縮，神経筋疾患による筋力低下・筋萎縮のメカニズムを，神経筋シナプスを介した運動神経と筋の相互維持作用による維持システムを知ることで解明したいと考えている．もともと健常筋には萎縮へと向かうカスケードが常在している．適切な運動習慣により，シナプスを介した筋と運動神経の相互作用システムが，萎縮カスケードに拮抗することで筋と運動神経の両方が保持されている．この筋と運動神経の相互作用を阻害する原因が，運動機能システムのいずれかの場所で発生すると筋萎縮が誘導される．私たちは，原因不明であった重症筋無力症の発症メカニズムを明らかにする過程で，シナプス筋側のシナプス襞先端部にアセチルコリン受容体（AChR）と凝集して発現しているMuSK蛋白（muscle-specific kinase：受容体型リセプター型タイロシンカイネース）が，運動神経終末と筋側の相互作用に必要な分子であることを明らかにした．

高齢社会を背景に重症筋無力症（myasthenia gravis：MG）の患者数が我が国でも増加していることが，2006年に実施された厚生労働省の免疫性神経疾患に関する調査で明らかになった．18年前の全国調査に比べ総数で2.5倍（いずれも推定で6,000人から1万5,100人へ），10万人当たりの有病率も5.1人から11.8人へと増えている．欧米では1990年代になってから，50歳以上の年代で予想されたよりも多くの患者が見つかるようになった．2005年には長野県で25年前に比べ，65歳以上の患者の罹患率が10～15倍に増加していることが報告されたのをはじめ，デンマーク，イタリア，ギリシャなどでも同様の報告が発表された[1]．高齢者のMG診断では，眼瞼下垂，複視，構音障害，嚥下困難を含む筋力低下などのMGに特徴的な症状が，若年者に比べ見過ごされ

A neuromuscular junction disorder and muscle weakness

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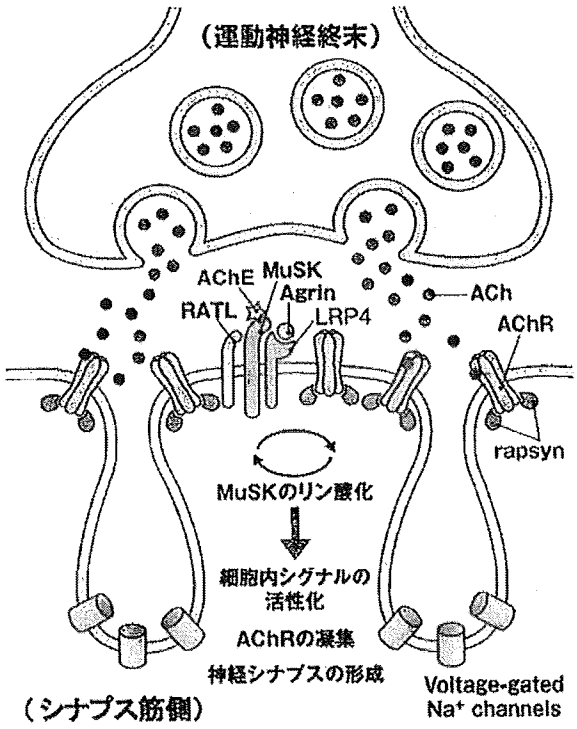

図1　神経筋シナプス接合部の模式図
運動神経終末から分泌されるagrin(ヘパラン硫酸プロテオグリカン)とLRP4（LDL受容体）がMuSKと結合した結果，MuSKが2量体を形成して細胞内領域にあるカイネースが活性化する．そして，お互いの細胞内領域をリン酸化することにより，様々なシグナル分子が結合し，細胞外から細胞内へシグナル伝達されAChRの凝集や核へ転写活性化シグナルを伝える．MuSKはAChE (acetylcholinesterase) のアンカー分子である．MuSKに結合するシグナル蛋白としてDok-7 (downstream of kinase) が同定された．Agrinは，直接MuSKと結合することができない．Rapsynは足場蛋白としてAChRと結合している．MuSKとAChRがシナプス襞に共凝集していることから，rapsynとMuSKを結ぶ蛋白としてRATLが想定されているが同定されていない．

がちになる．そして，MGがアセチルコリンレセプター（AChR）抗体だけでなく，muscle-specific（MuSK）抗体でも発症することが明らかとなった今，MGが疑われる患者に対してはMuSK抗体も測定する必要がある．本稿では，MuSK抗体陽性MG（MuSK-MG）を中心に最近の知見を紹介する．

MuSK抗体の発見と病原性の証明

30年前のAChR抗体の発見以来，自己抗体が不明の10～20%の全身型MG患者も血漿交換で症状が改善されることや，患者抗体をマウスの腹腔に投与すると筋電図に変化が検出できることから，未知の抗原に対する自己抗体でMGが発症することが予想された[2][3]．しかし，その抗原については約30年間まったく手がかりがつかめなかった．2001年Hochらは，全身型AChR抗体陰性MG患者の70%でMuSK抗体が陽性になることを報告し[1]，その他のグループも同様にMuSK抗体が陽性となる患者群が存在することを確認した[2][3]．2006年，筆者らはウサギを使った動物実験によりMuSK抗体でMGが発症することを最初に報告した[5]．続いてHochらはマウスを使い異なる動物種でもMuSK抗体でMGが発症することを確認した[6]．さらに今年Coleらにより，MuSK抗体陽性患者のIgG分画をマウス腹腔に投与したpassive transfer実験で，マウスにMGを発症することが明らかとなった[7]．「MuSK抗体でMGが発症する」という概念は今や確立されたと言ってよいであろう．

MuSKとは何か？

MuSKはレセプター型タイロシンカイネースに分類され神経筋シナプスの筋側で，シナプス襞の先端部にAChRとともに凝集して集積している（図1）．胎児の発生期，神経筋シナプスのAChR集積とシナプスの形態形成にMuSKが必要であることが，ノックアウトマウスを使った研究で明らかにされた[8]．また著者らは，MuSKが成体の神経筋シナプスの維持にも必要であることを示した[5][9][10]．MuSKの細胞外領域に，運動神経終末由来のagrinと未知の分子が結合することにより細胞内のタイロシンカイネース酵素の部位を活性化させてMuSK機能が調節される[11]．MG患者のMuSK抗体はこの機能を抑制すると考えられる[5][9][10]．

MuSK抗体陽性MG患者の臨床的特徴

1．MuSK抗体陽性MGの疫学

神戸薬科大学，国立病院機構宇多野病院と共同でMuSK抗体の鋭敏な測定方法を開発した．宇多野病院の結果と他の報告を加え集計すると，本邦ではAChR抗体陰性患者の30.7%（27/115）がMuSK抗体陽性である[12]．また，欧米の報告を集計すると38%（247/648）で日本より頻度が高い[13]．米国では，白人系よりもアフリカ系にMuSK抗体MGの患者が多い傾向にある[14]．また，Vincentらは地球上南北の高緯度の国ほど発症頻度が少なくなると報告しており，これは人種の違いだけでは説明できないことからMuSK-MGの発症に何らかの環境要因も存在することが予想されている[14]．MuSK-MG患者の男女比を見ると，日本では1：3.6（5：18），欧米は1：5.1(25：127)でともに女性の割合が多い[12][15]．