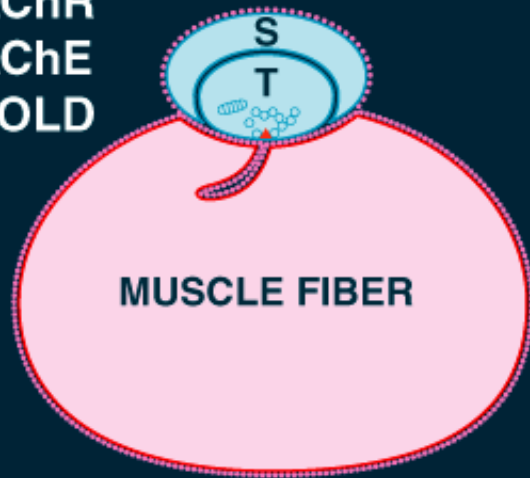


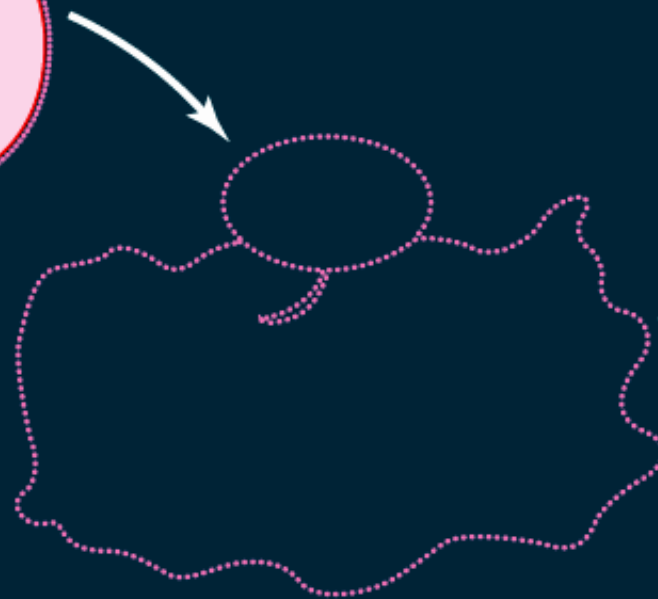
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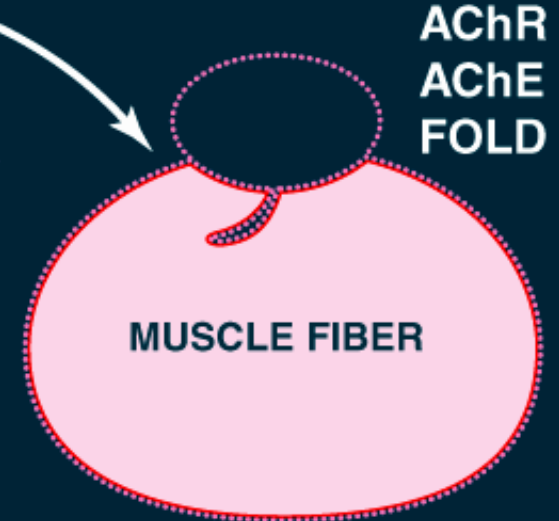
AChR  
AChE  
FOLD



DEGENERATION



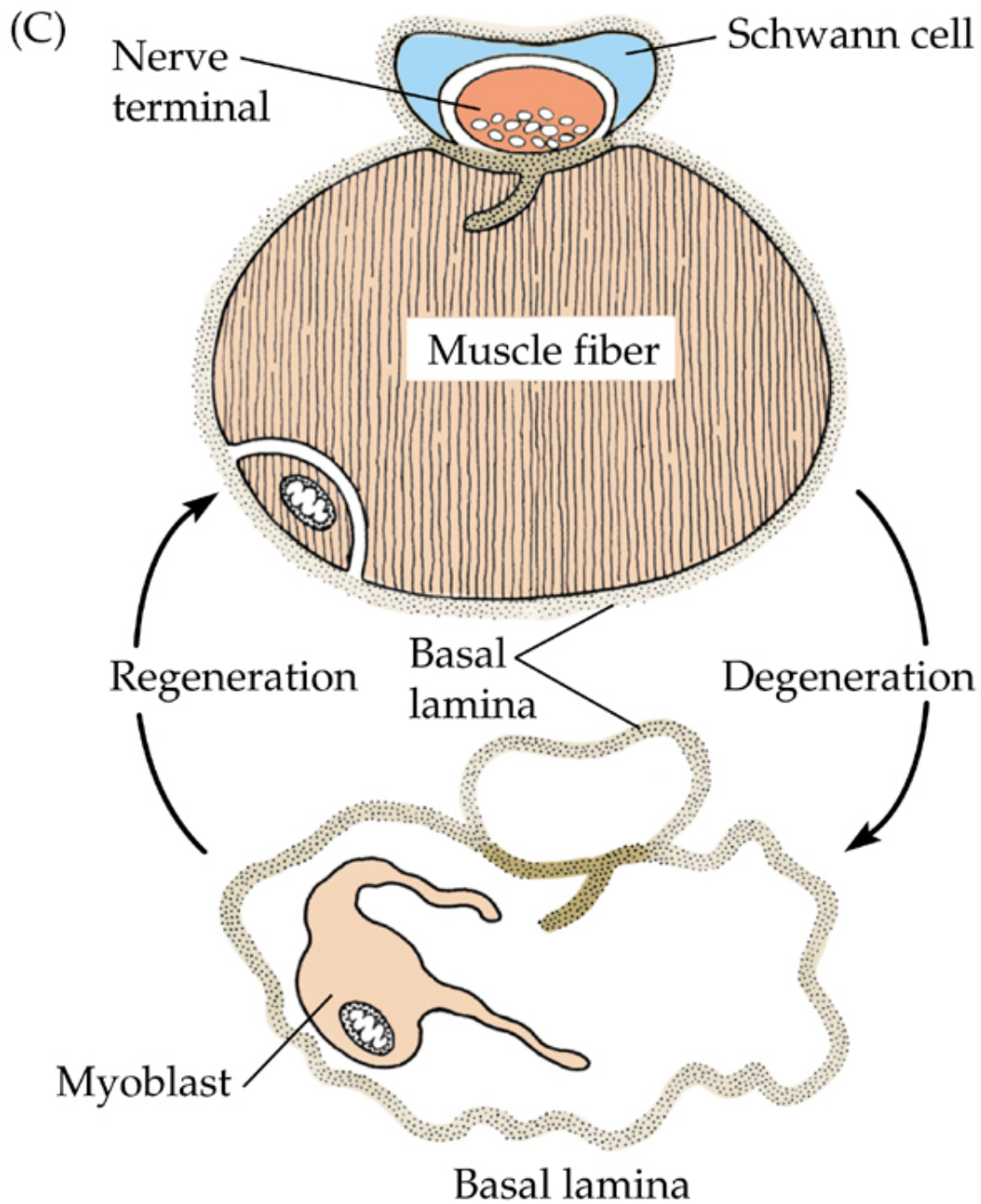
REGENERATION

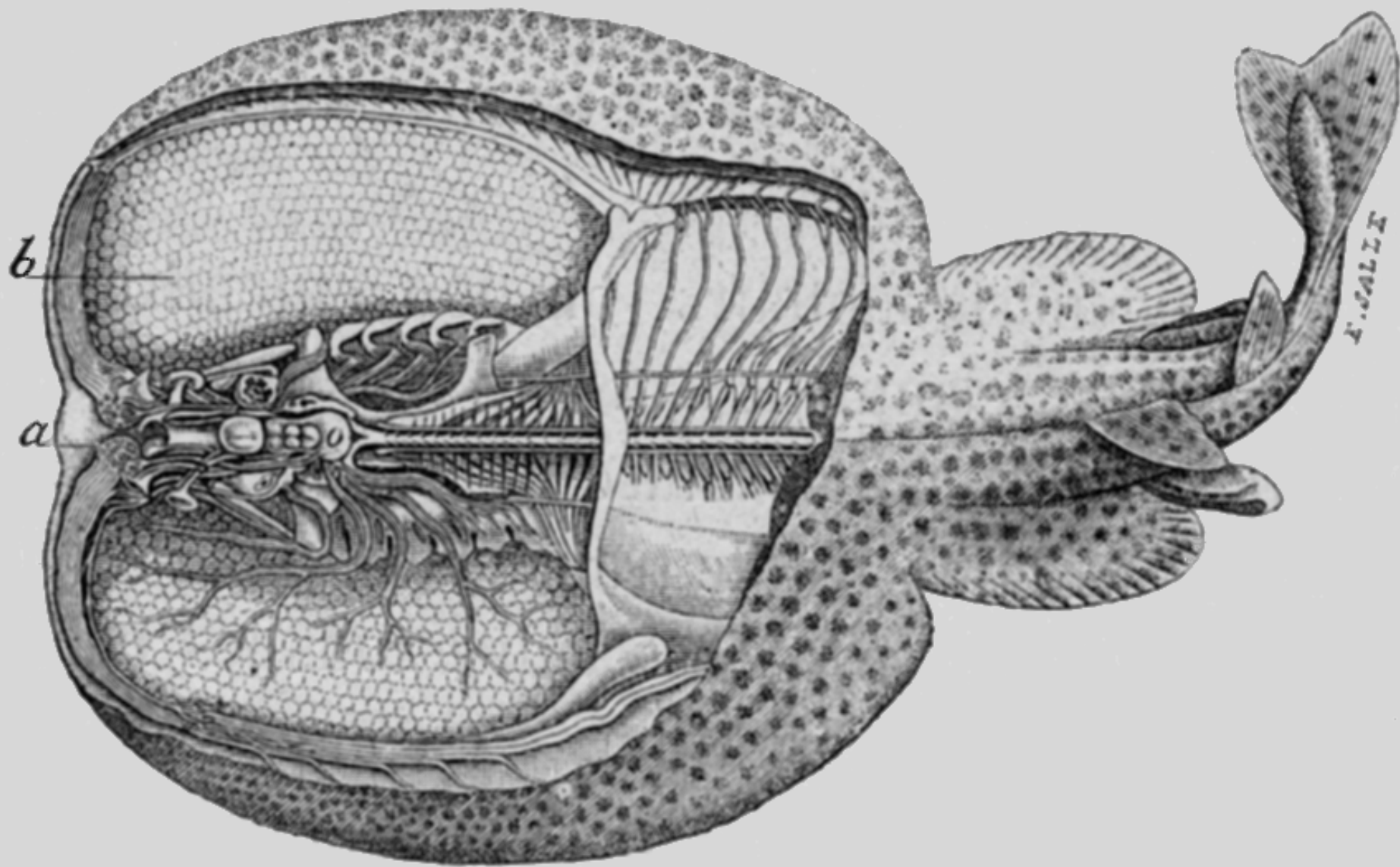


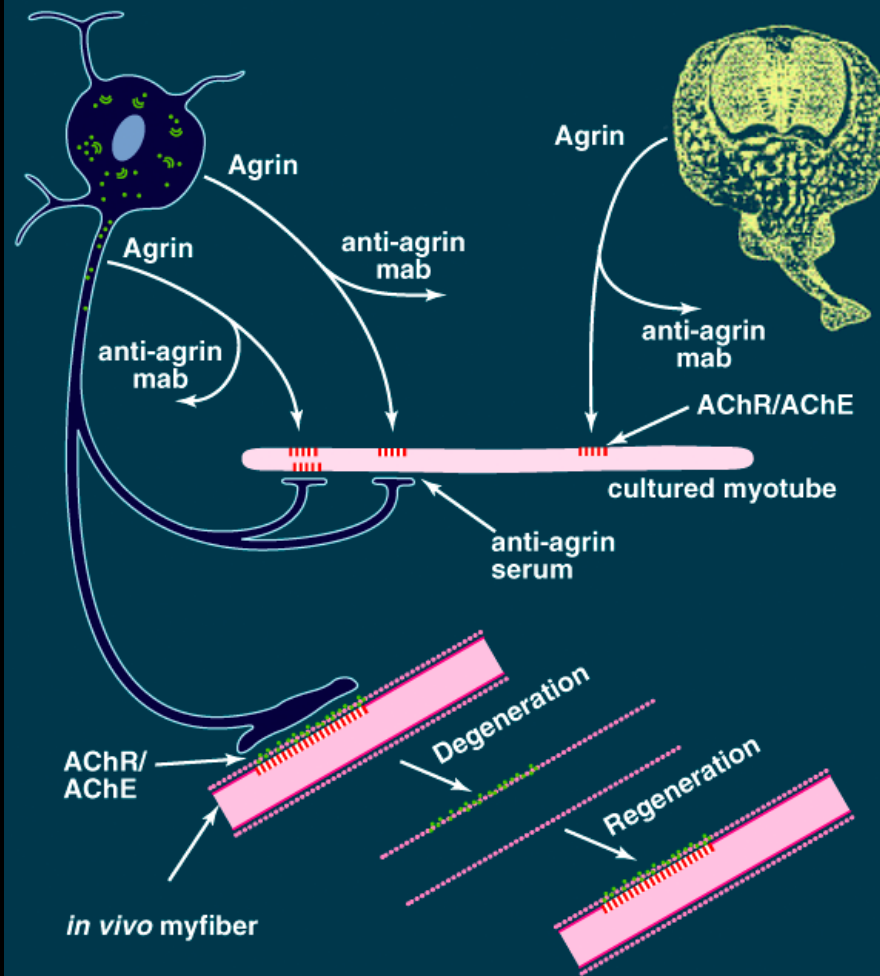
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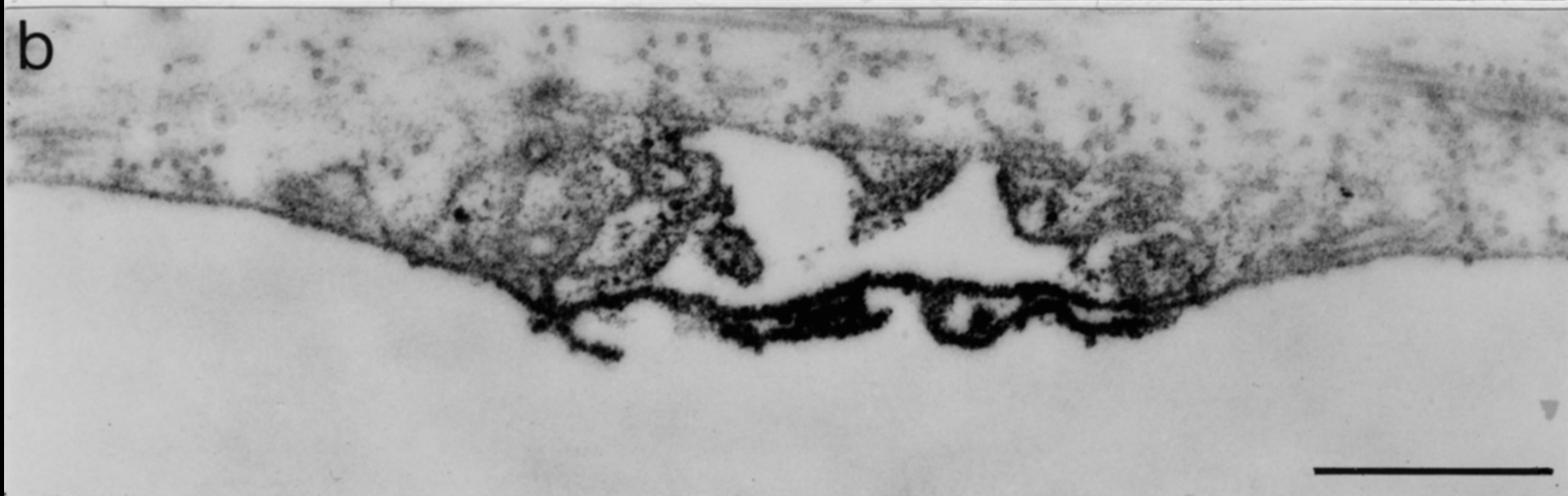
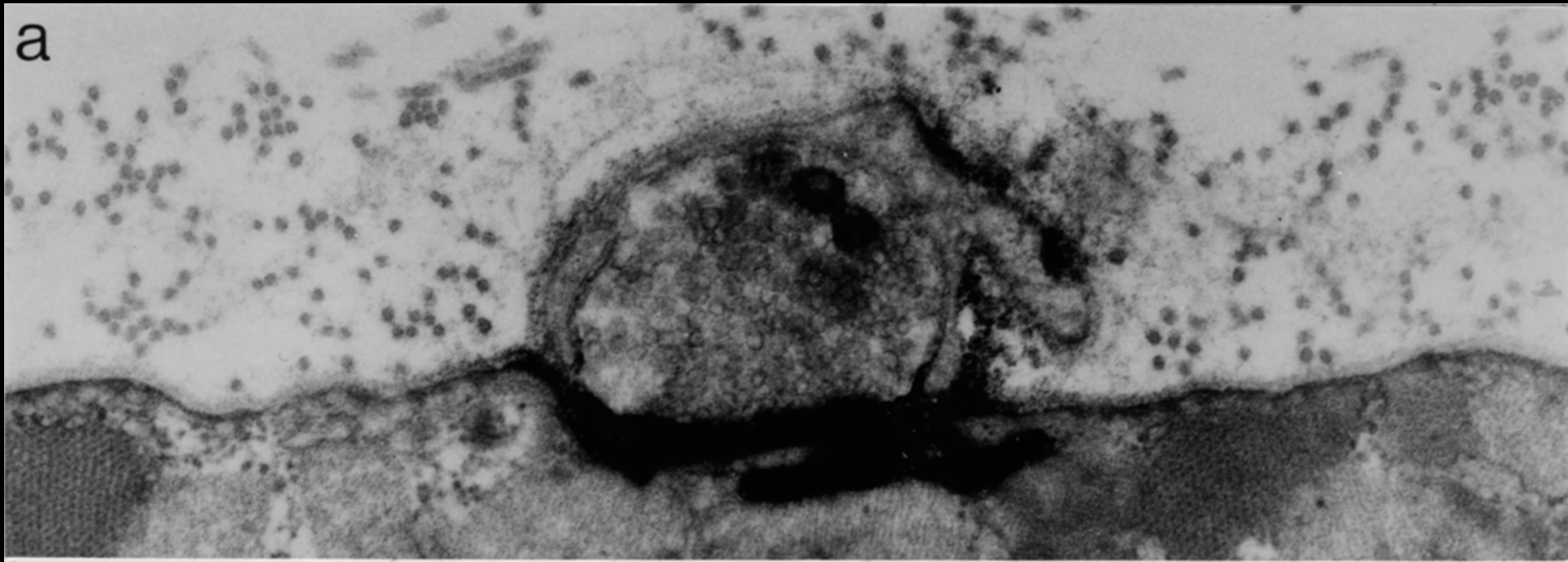
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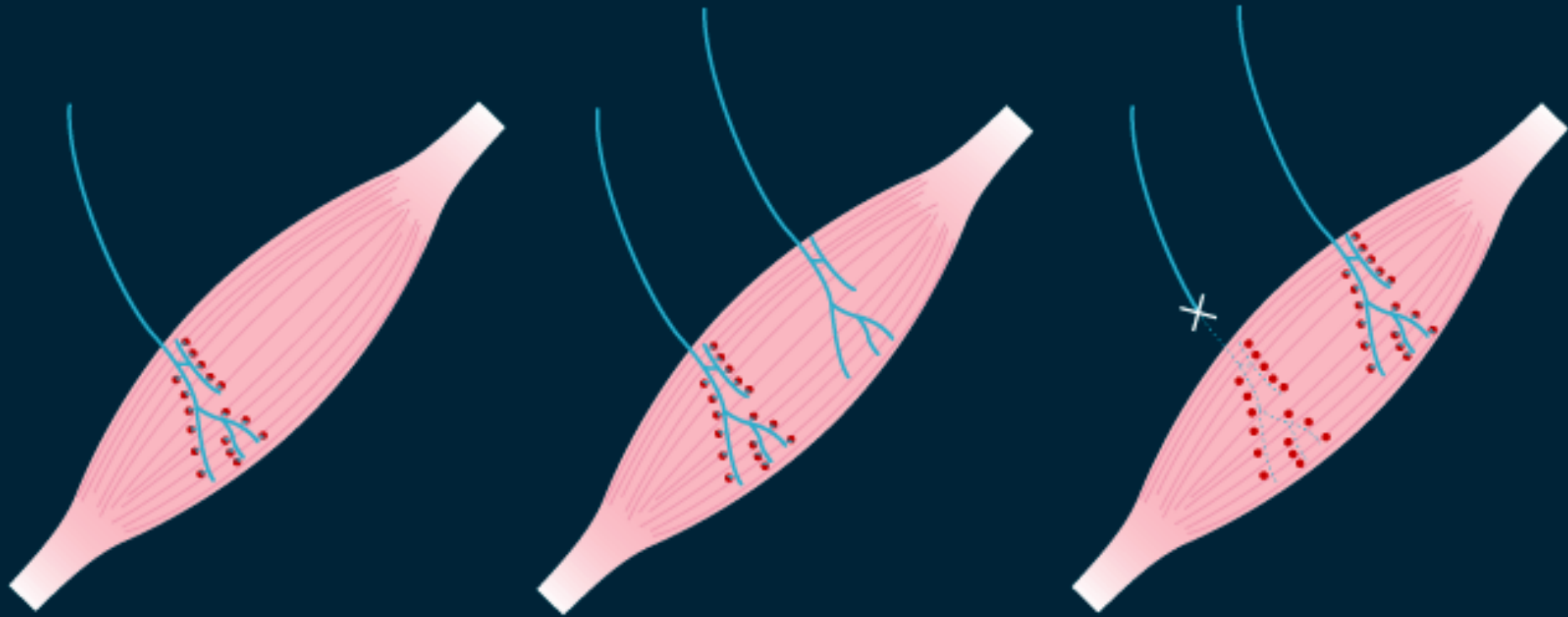
Ruegg, Tsim, Horton, Kroger, Escher  
Gensch, McMahan  
Neuron 8: 691-699 (1992)

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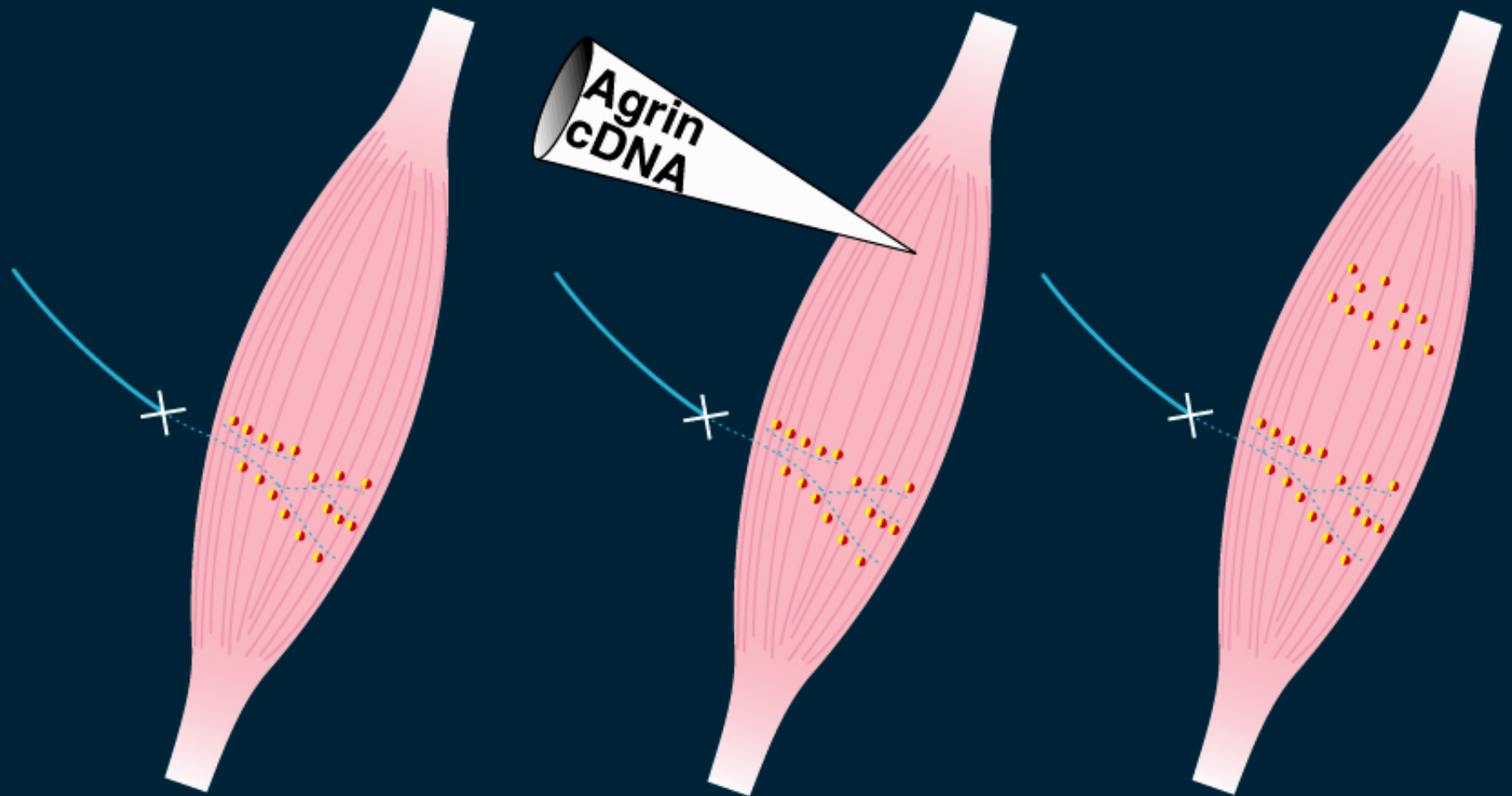
Elsberg (1917), Fex and Thesleff (1967), Lomo and Slater (1978)



*McMahan / Colyear '97*



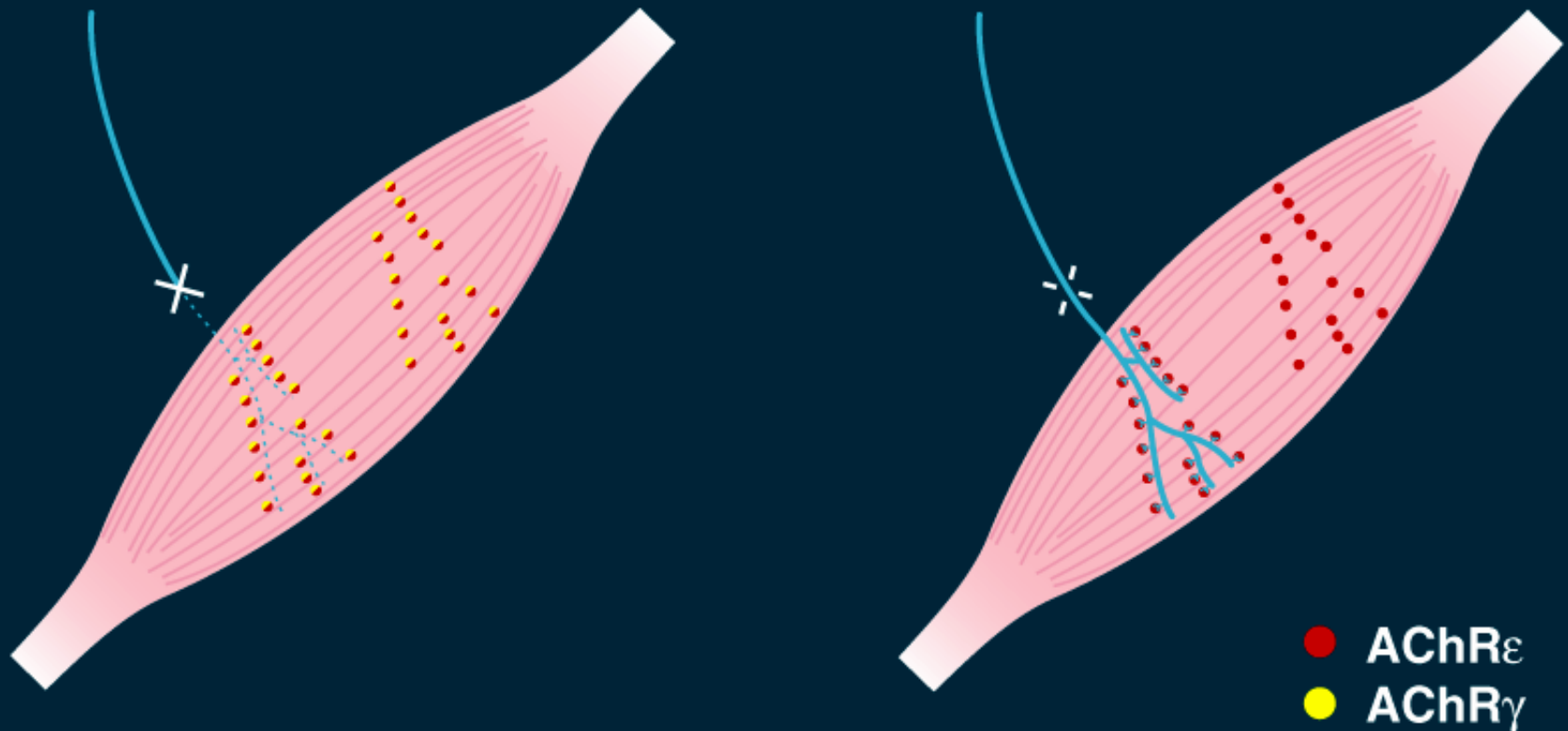
## Agrin-induced Postsynaptic-like Apparatus in Denervated Soleus Muscles



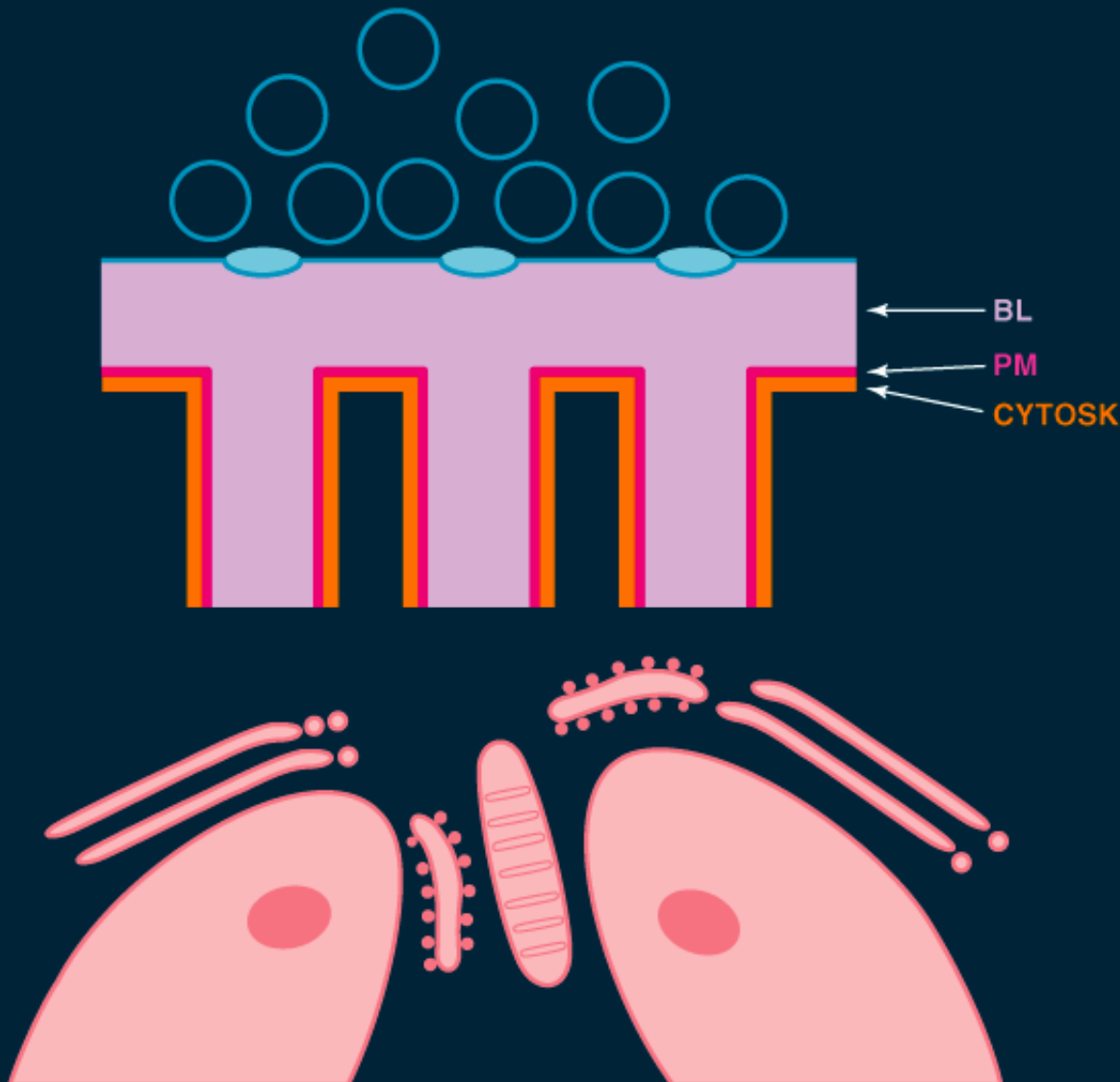
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McMahan / Colyear '98

## AChR Subtypes in Agrin-induced Patches in Denervated and in Reinnervated Soleus Muscles



# Axon-induced Postsynaptic Apparatus

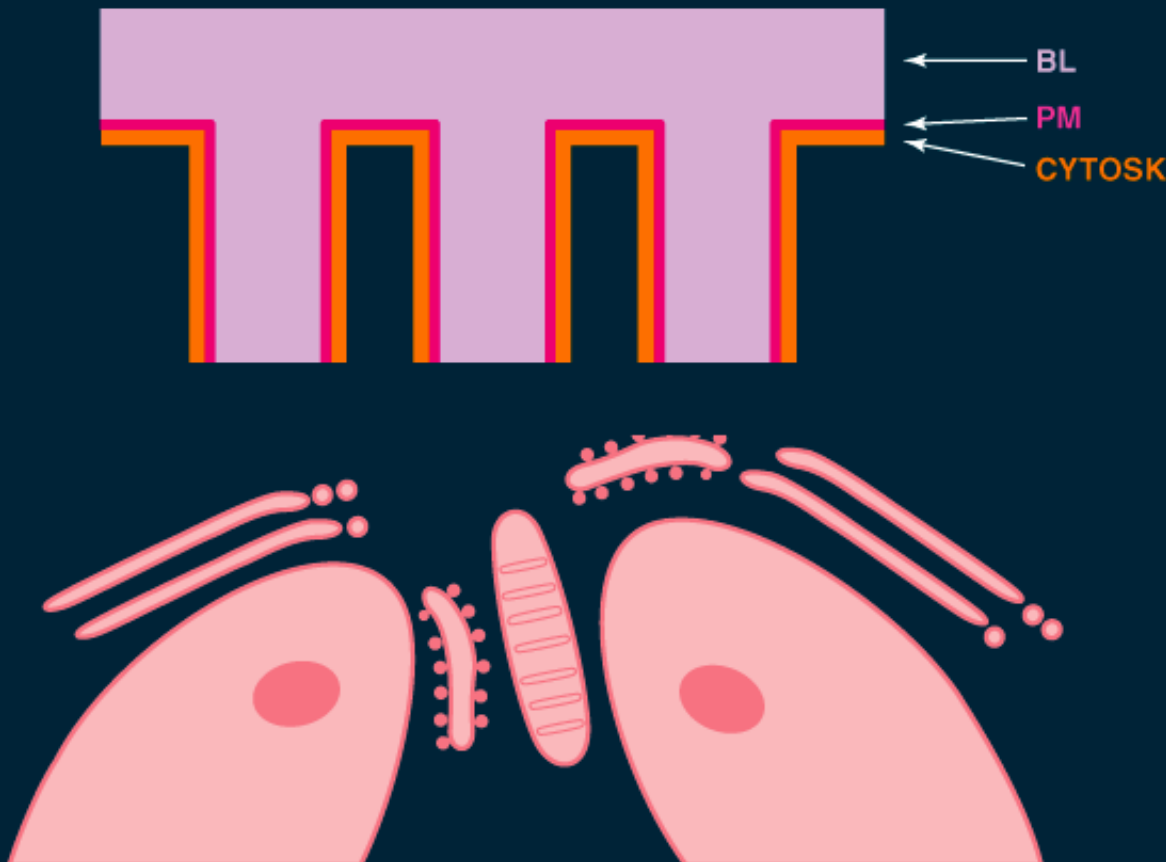


**Basal Lamina**  
 acetylcholinesterase  
 agrin  
 collagens  
 heparin sulphate proteoglycan  
 laminin A  
 neuregulin  
 s-laminin

**Postsynaptic Membrane**  
 acetylcholine receptor  $\epsilon$   
 neuregulin A  
 erb B receptors 2, 3 & 4  
 integrin  
 MuSK  
 N-CAM  
 sodium channels

**Cytoskeleton**  
 rapsyn  
 vinculin  
 talin  
 paxillin  
 filamin  
 $\alpha$ -actinin  
 tropomyosin 2  
 58k protein  
 87k protein  
 utrophin  
 acetylated tubulin  
 ankyrin  
 lamin B  
 actin  
 $\beta$ -spectrin

# Agrin-induced Postsynaptic-like Apparatus



**Basal Lamina**  
acetylcholinesterase  
agrin  
collagens  
heparin sulphate proteoglycan  
laminin A  
neuregulin  
**s-laminin**

**Postsynaptic Membrane**  
acetylcholine receptor  $\epsilon, \gamma$   
neuregulin A  
erb B receptors 2 & 3  
integrin  
**MuSK**  
N-CAM  
sodium channels

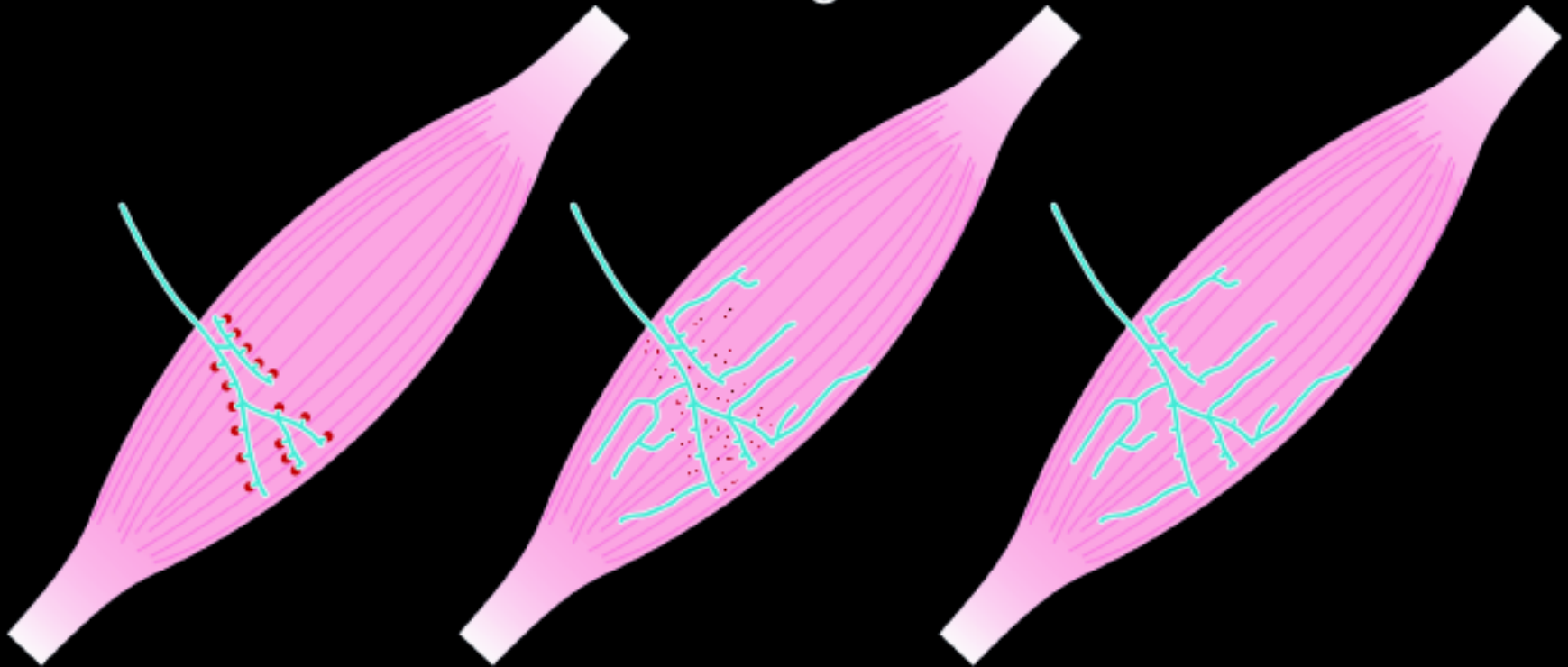
**Cytoskeleton**  
rapsyn  
vinculin  
talin  
paxillin  
filamin  
 $\alpha$ -actinin  
tropomyosin 2  
58k protein  
87k protein  
**utrophin**  
acetylated tubulin  
ankyrin  
lamin B  
actin  
 $\beta$ -spectrin

# GENE DELETION

$+/+$

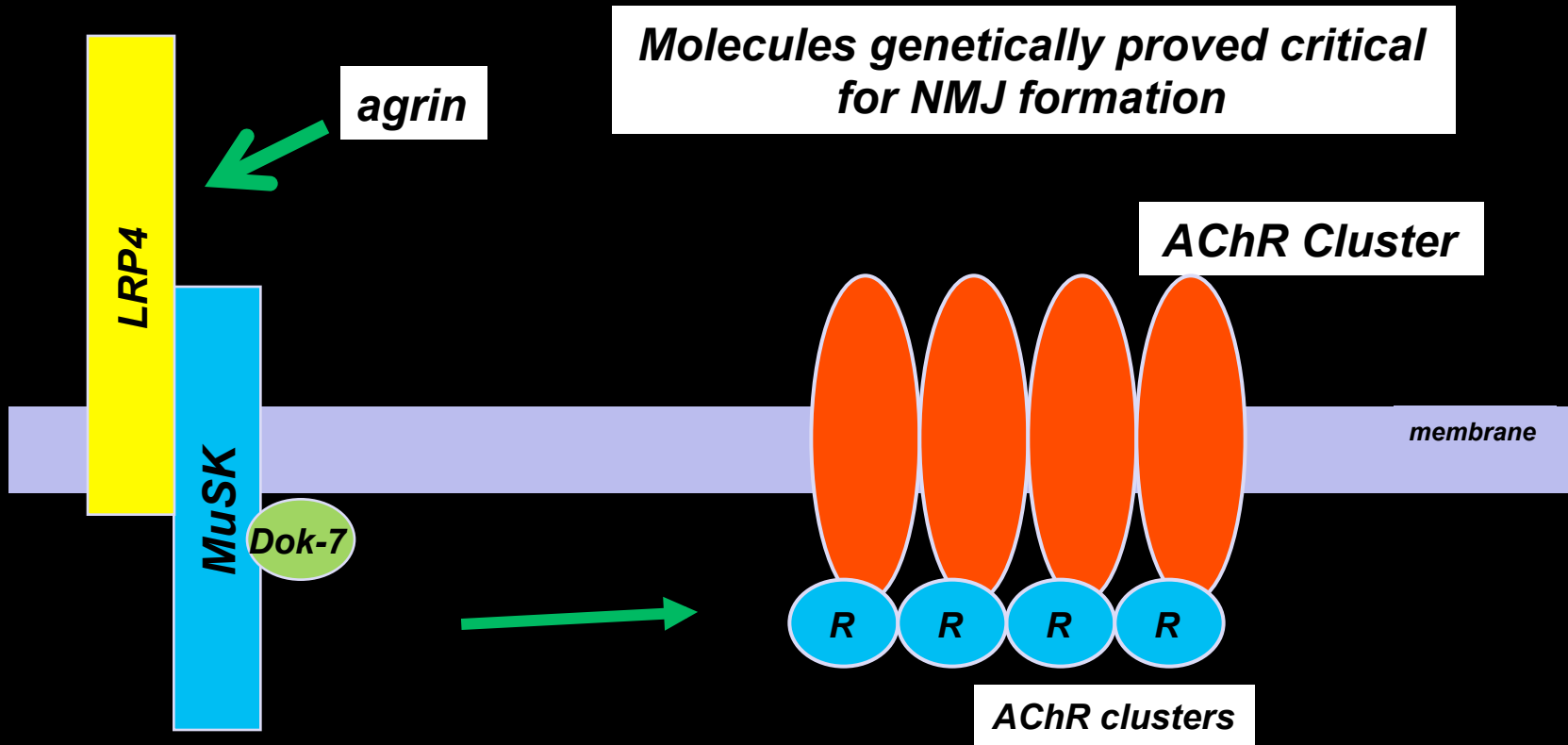
Agrin  $B^{+/-}$

MuSK  $^{-/-}$



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Scheller, Merlie, Sanes  
Cell, 85: 525-535, 1996.

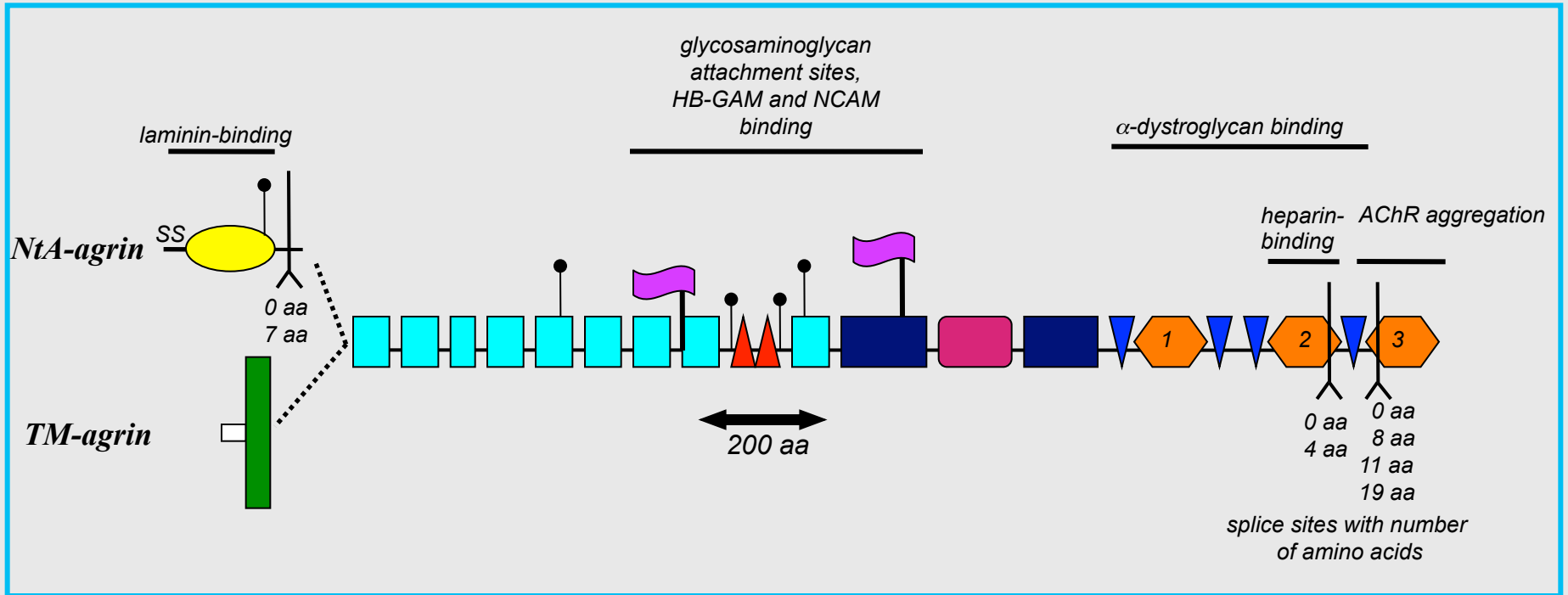
DeChiara, Bowen, Valenzuela, Simmons,  
Poueymirou, Thomas, Kinetz, Compton,  
Rojas, Park, Smith, DiStafano, Glass,  
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Cell, 85: 501-512, 1996.



**LRP4: Agrin Receptor, a member of the Low-density Lipoprotein Receptor Family**  
**MuSK: Muscle Specific Kinase**  
**R: Rapsin**



# Domain Structure of Agrin



□ *intracellular domain*

■ *transmembrane domain (TM)*

● *NtA-domain*

■ *follistatin-like domain*

■ *conserved GAG chain attachment site*

● *potential N-linked glycosylation site*

▲ *laminin EGF-like domain*

■ *Ser/Thr-rich region*

■ *SEA (sea urchin sperm protein, enterokinase and agrin) domain*

▼ *EGF-like domain*

◈ *laminin globular domain*

# ***AGRIN PATHWAY DISEASES***

## ***Neuromuscular Junctions***

### ***Autoimmune Myasthenia Gravis***

*Antibodies to MuSK and Lrp4 lead to pathogenesis in certain patients having AChR antibody-negative myasthenia gravis.*

### ***Congenital Myasthenia***

*Mutation in agrin*

*Mutation in MuSK*

*Mutation in Dok-7*

## ***CNS Synapses***

### ***Congenital Dementia***

*Mutation in neurotrypsin which degrades agrin*

