What every MG patient should know

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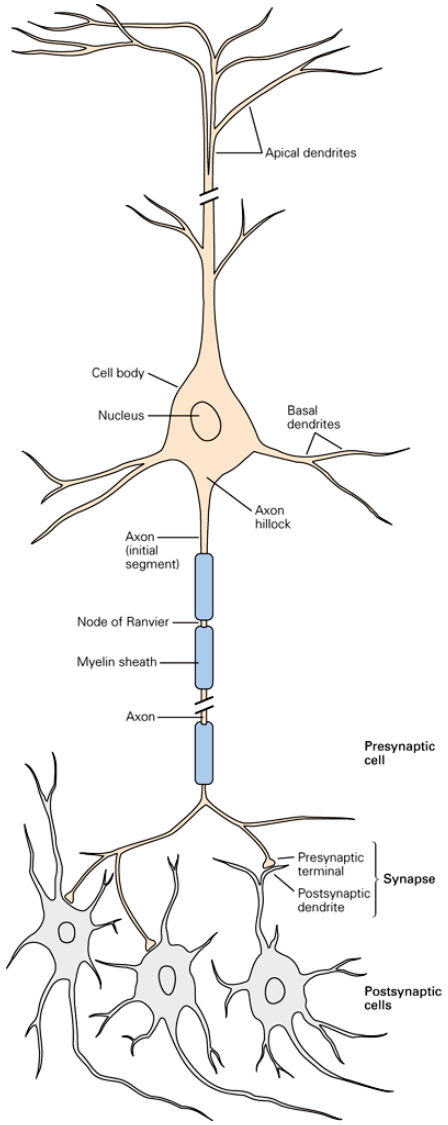
Part I: What is MG?

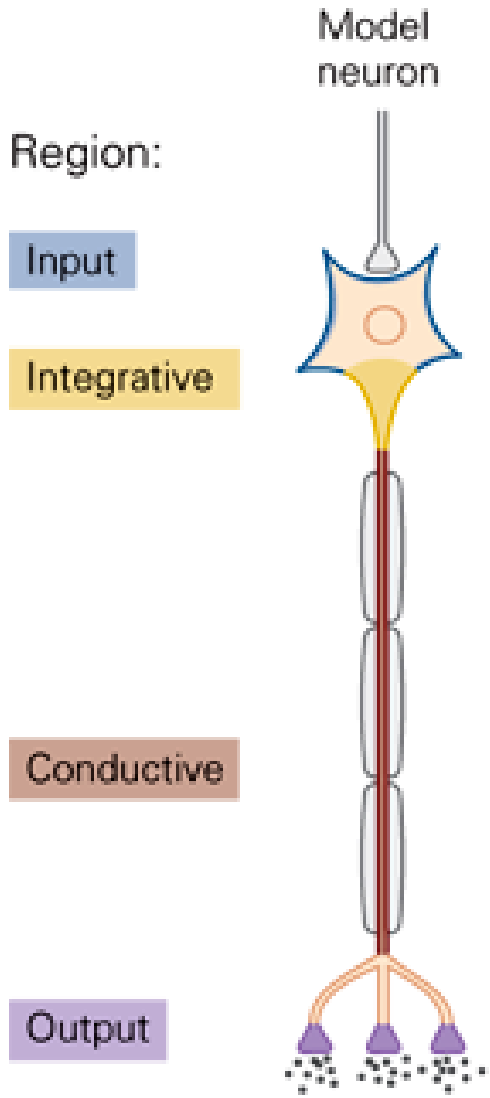
- “Autoimmune disease caused by antibodies against AChR and other related molecules on the post-synaptic side of the neuromuscular junction”

- MG is also the best understood antibody-mediated neurologic disease

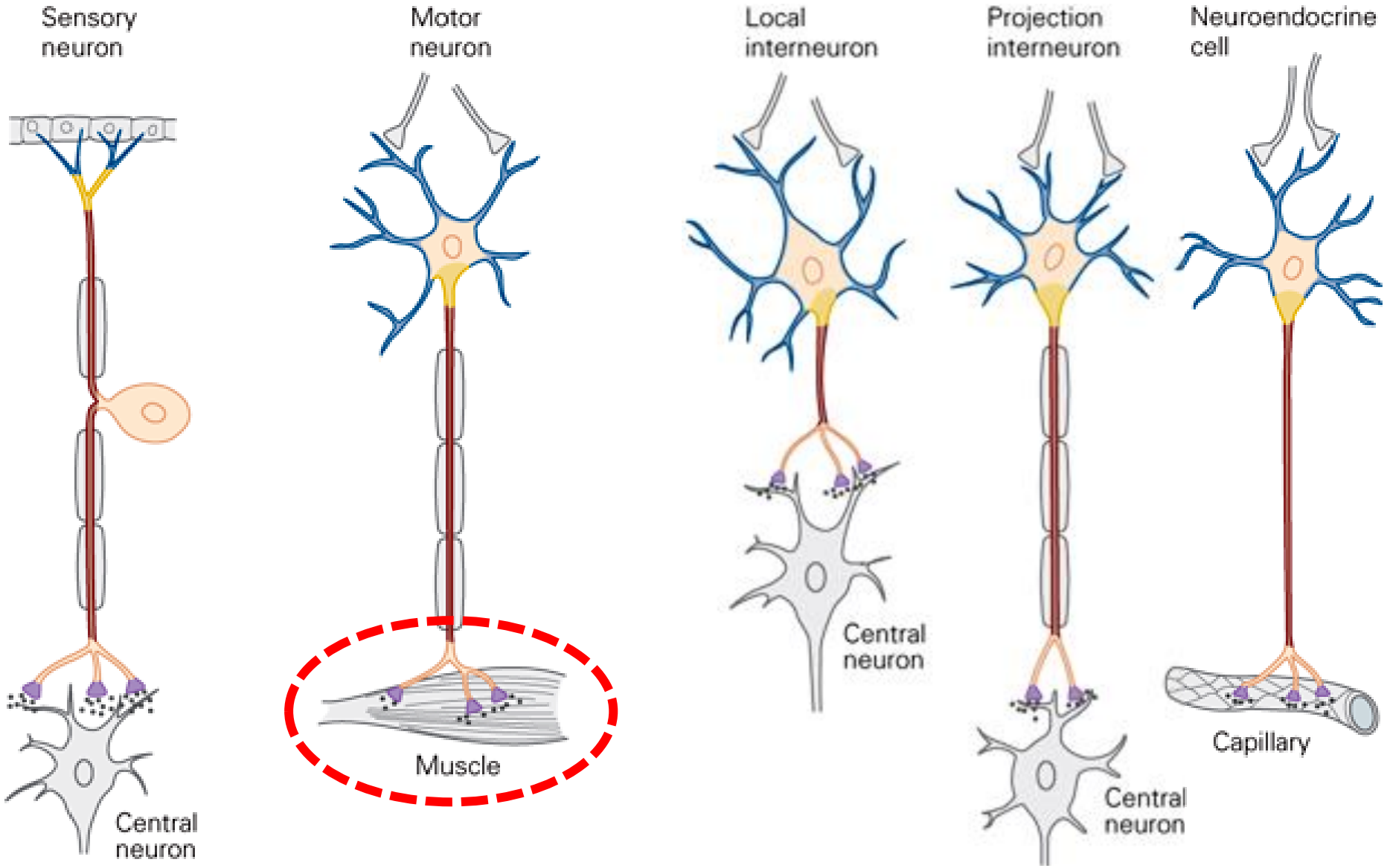
1. Localization in the nervous system of the problem?
2. Cause: what is the cause?

Localization

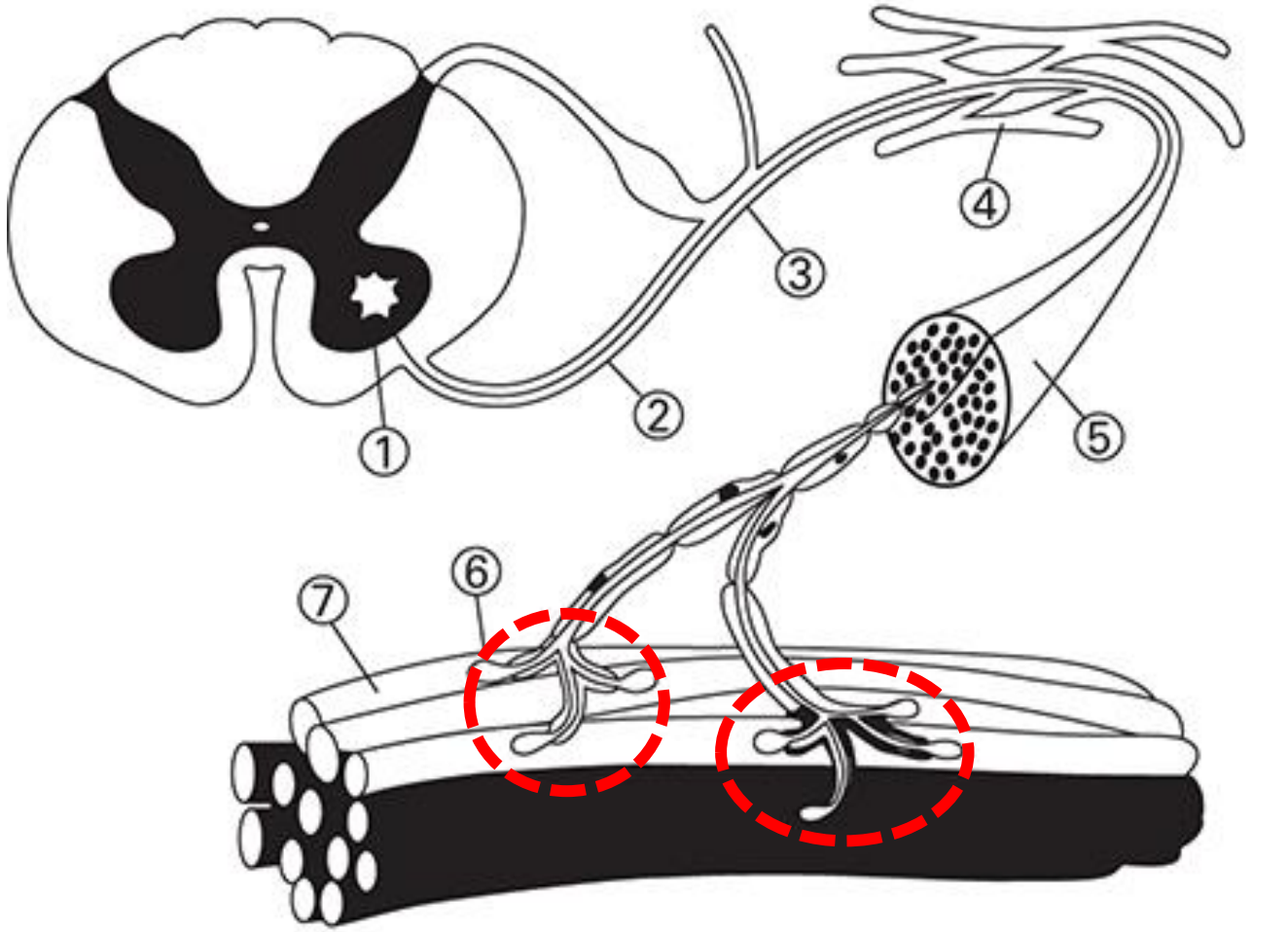




Kandell, Schwartz, Jessell, Siegelbaum and Hudspeth. Principles of Neural Science Fifth Edition Fig 2-1 and 2-9

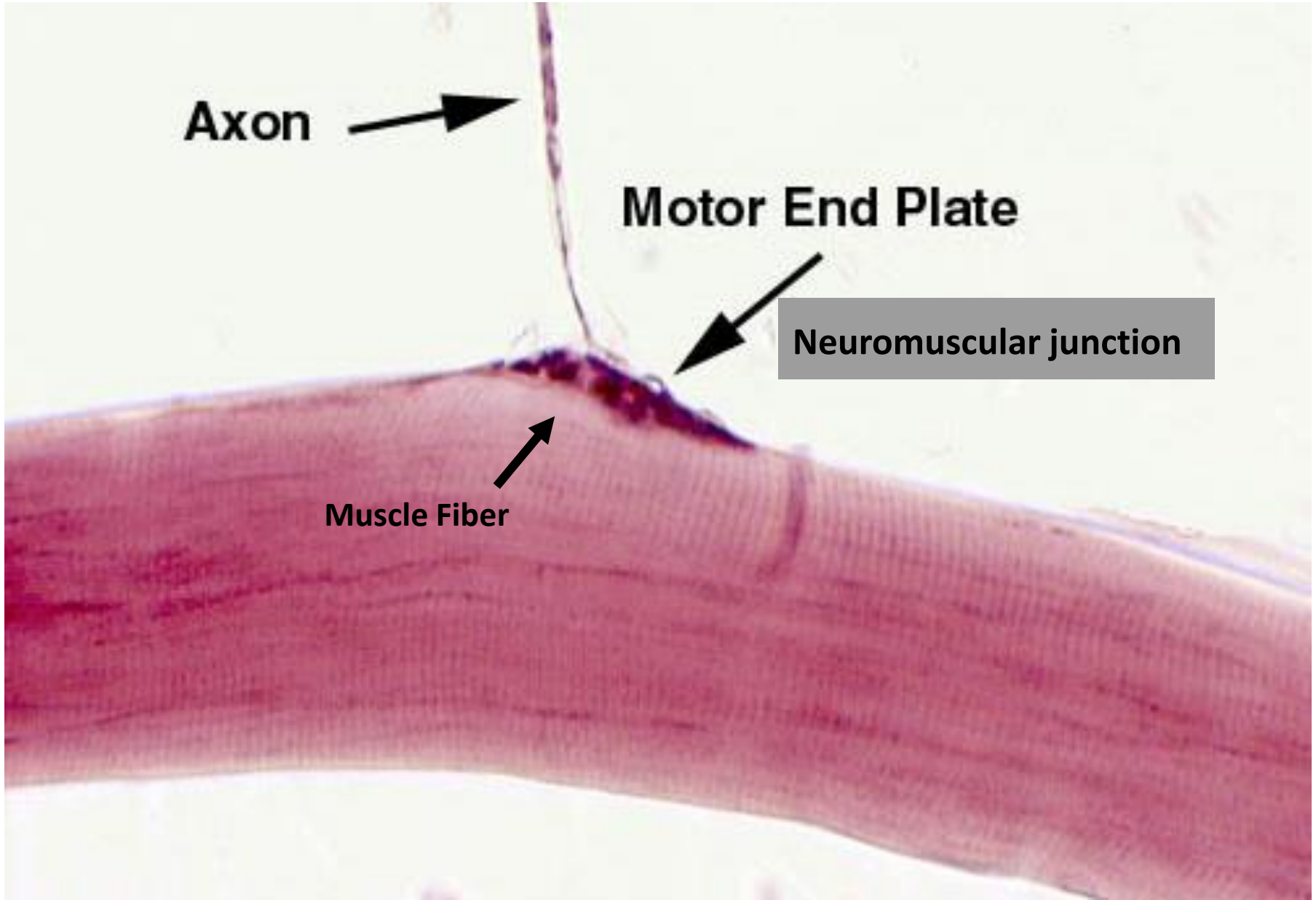


Kandell, Schwartz, Jessell, Siegelbaum and Hudspeth. Principles of Neural Science Fifth Edition Fig 2-9

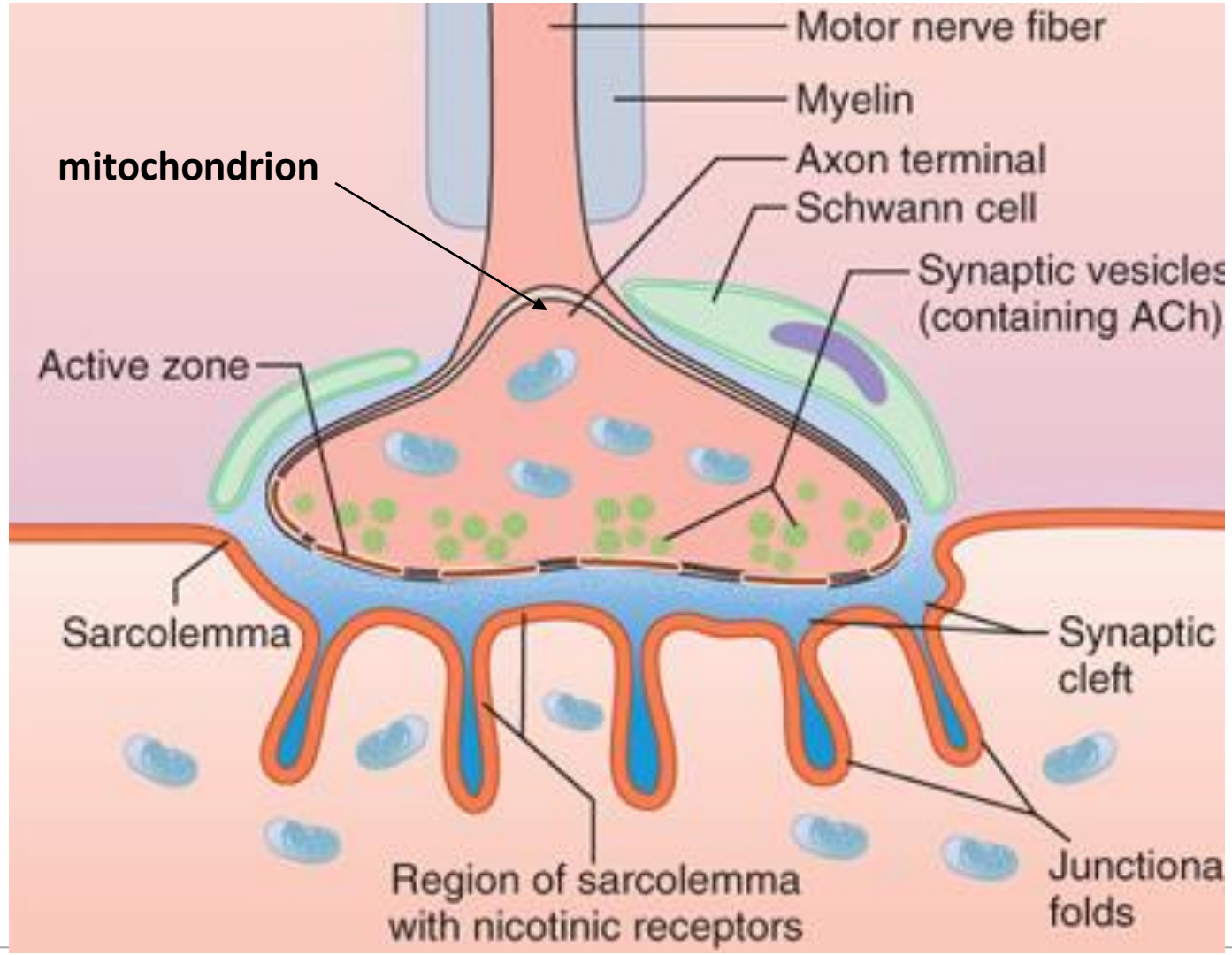


1. Anterior horn cell
2. Nerve root
3. Spinal nerve
4. Plexus
5. Peripheral nerve
6. Neuromuscular junction
7. Muscle fiber

Light electroscope image

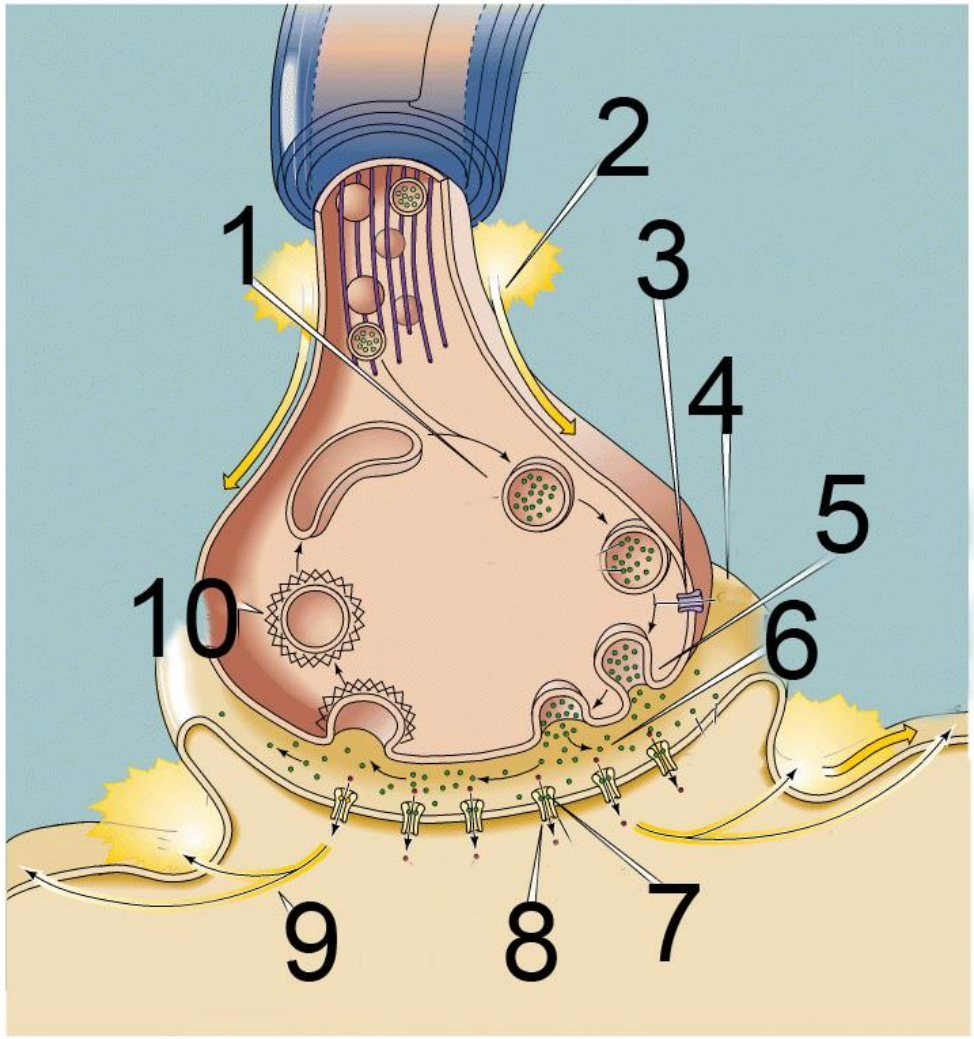


The neuromuscular junction: the specialized synapse between nerve and muscle



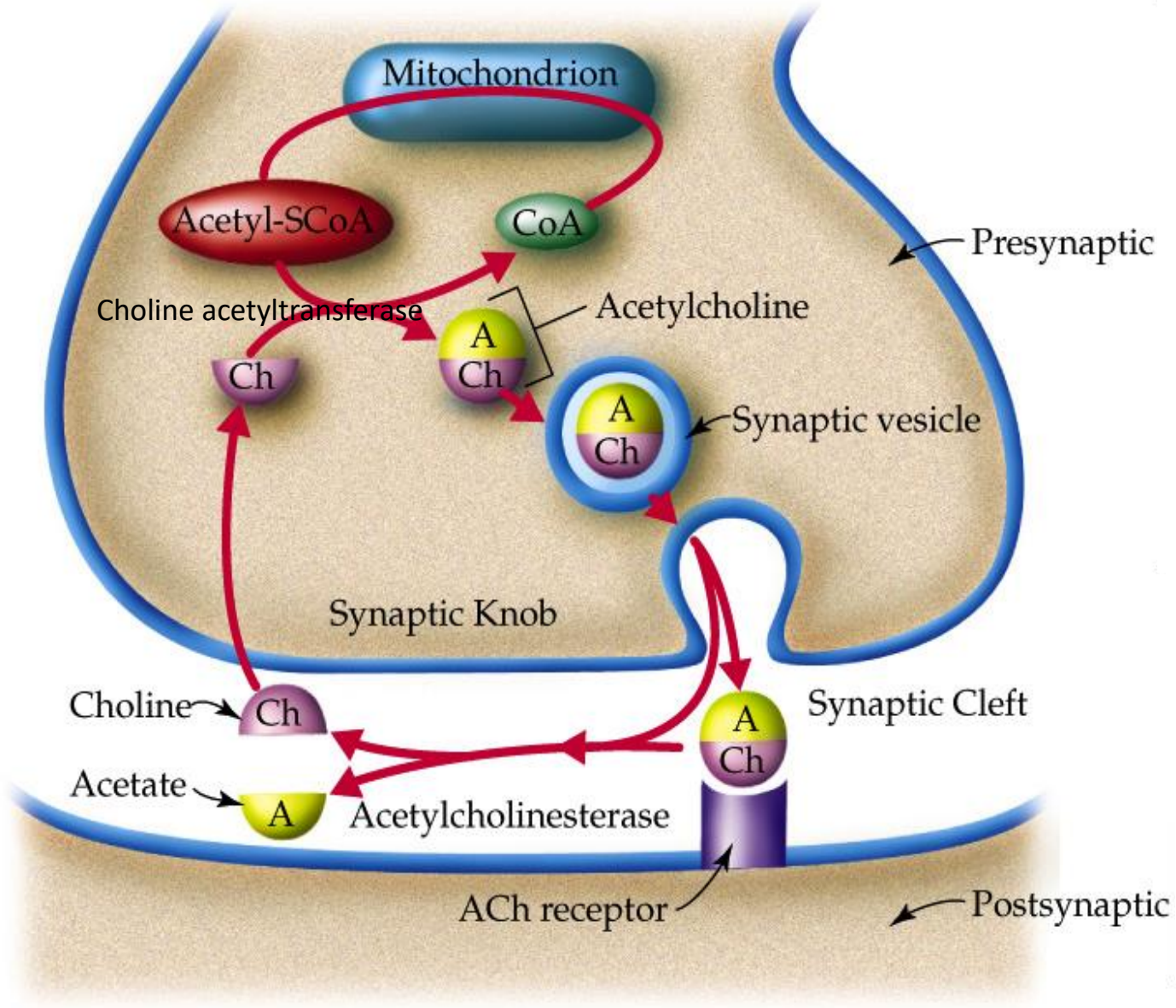
Citation: Synaptic & Junctional Transmission, Barrett KE, Barman SM, Boitano S, Brooks HL. *Ganong's Review of Medical Physiology, 25e;* 2018. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=1587&sectionid=97162680&jumpsectionid=97162706 Accessed: May 14, 2019

Transmission across a typical chemical synapse

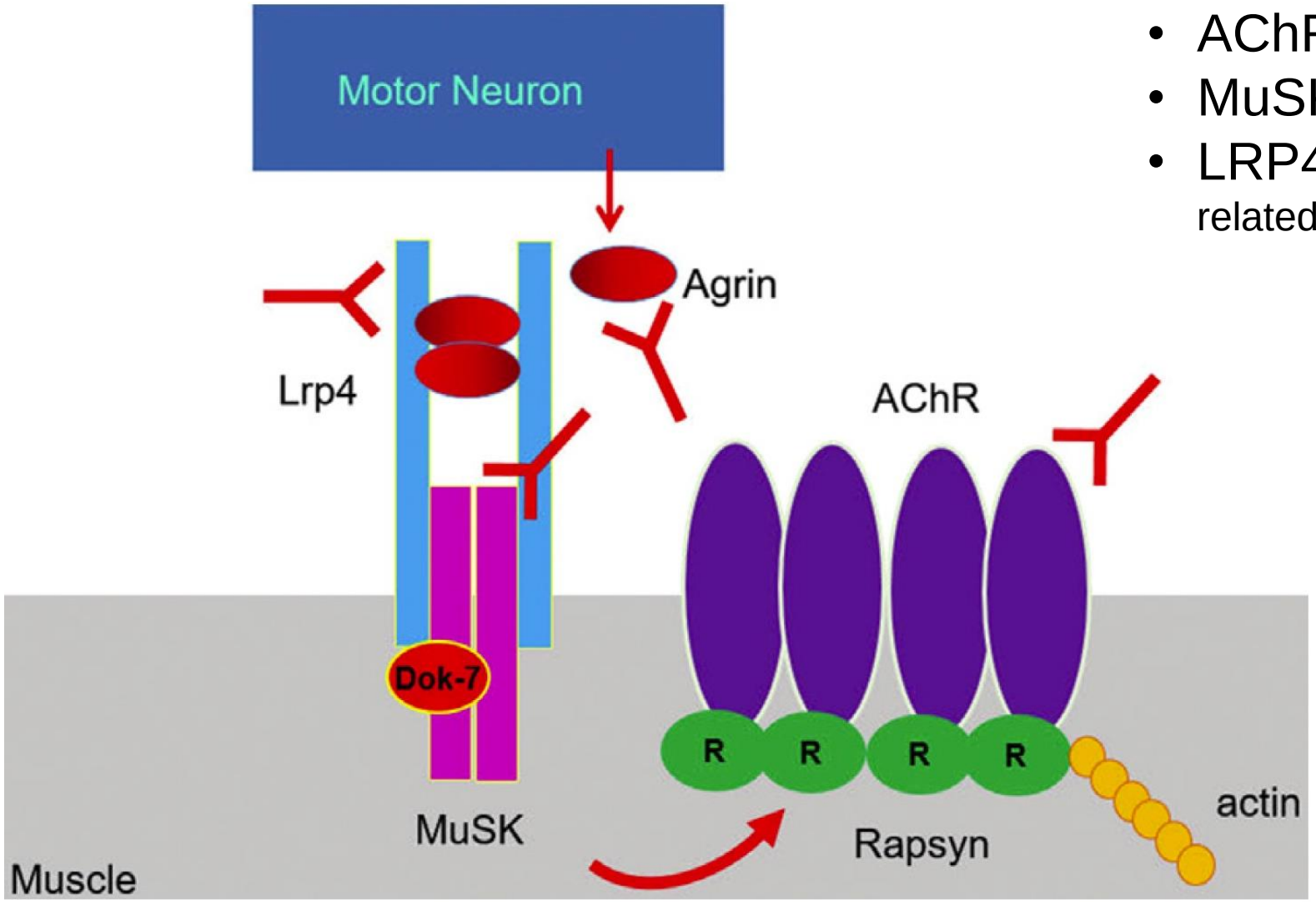


Neuroscience 2nd Ed. Fig. 5-3
By Purves et al., NCBI Entrez / Bookshelf
http://www.ncbi.nlm.nih.gov/books/NBK11009/

Acetylcholine synthesis and synaptic digestion at the NMJ

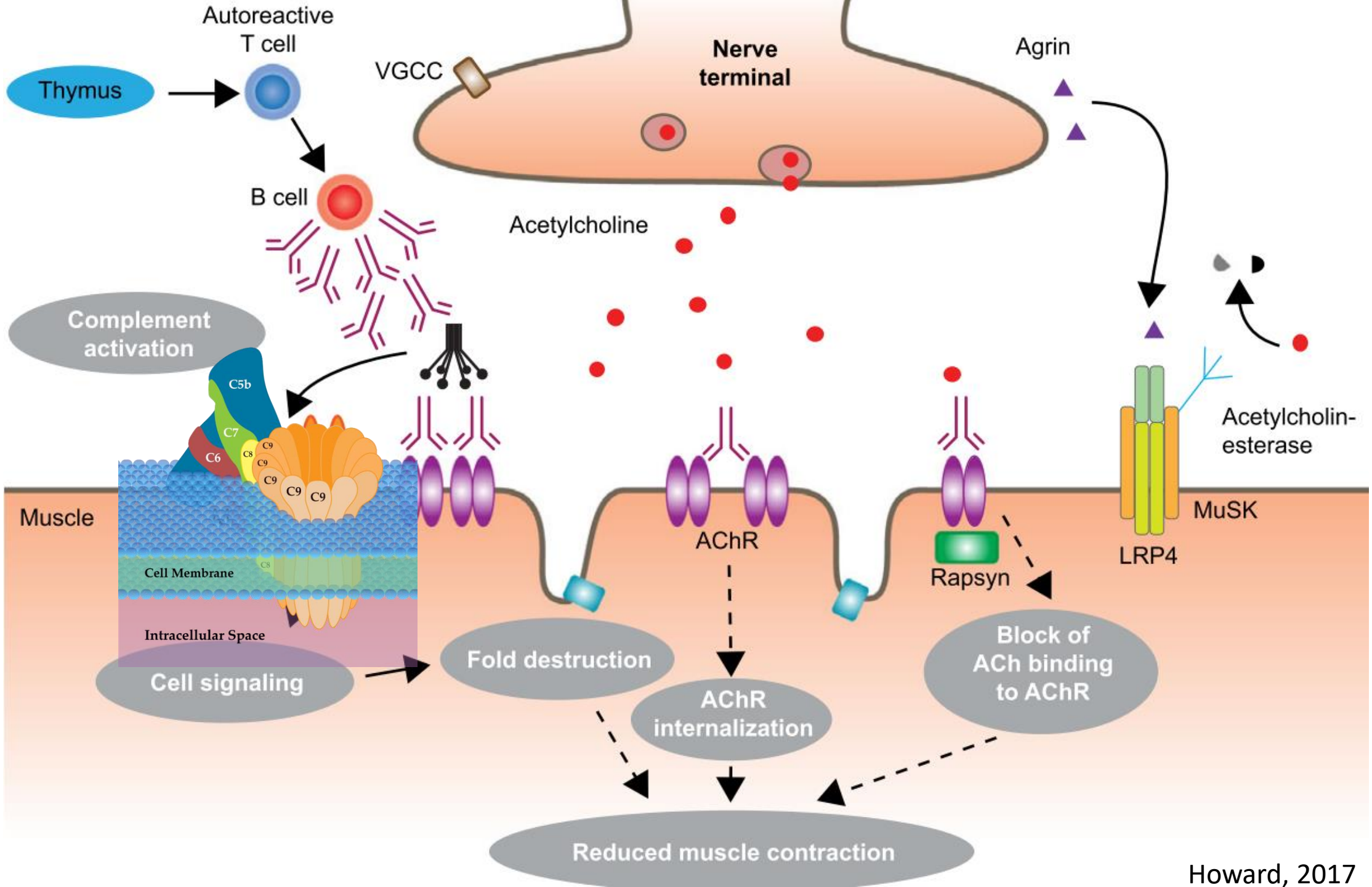


Cause: Autoantibodies in MG



- AChR (acetylcholine receptor)
- MuSK (muscle-specific tyrosine kinase)
- LRP4 (low-density lipoprotein receptor-related protein 4)

Rivner, M. H., Pasnoor, M., Dimachkie, M. M., Barohn, R. J. & Mei, L. Muscle-Specific Tyrosine Kinase and Myasthenia Gravis Owing to Other Antibodies. *Neurologic clinics* **36**, 293-310 (2018).


Autoreactive
T cell
Thymus
VGCC
Nerve
terminal
Agrin
B cell
Acetylcholine
Complement
activation
C5b
C7
C6
C8
C9
C9
C9
C9
C9
Cell Membrane
Intracellular Space
Muscle
AChR
Rapsyn
LRP4
MuSK
Acetylcholin-
esterase
Cell signaling
Fold destruction
AChR
internalization
Block of
ACh binding
to AChR
Reduced muscle contraction

Howard, 2017

Differentiating features in MG

Clinical manifestations

Age of onset

Antibody status

Thymic pathology

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Classification of MG subgroups

- **Late-onset MG**: age>50, slightly more common in men, AChR Ab+
- **Early-onset MG**: age<50, 3:1 women, AChR ab+, may be harder to control dz
- **Thymoma MG**: paraneoplastic, 10% of MG, always AChR Ab+, more severe
- **MuSK MG**: Rare (5%), predominantly bulbar features, rituximab use more now
- **LRP4 MG**: Rare, predominantly ocular, milder phenotype,
- **(Triple) seronegative MG**: 10% if patients, diagnostic challenge, (exam, RNS, SFEM
- **Ocular MG**: ptosis, eye movement weakness; harder to diagnose, prednisone works

Treatment resistant MG: 10-15% resistant to prednisone and other immune therapy; or can't tolerate side effects; or long term IVIG/PLE

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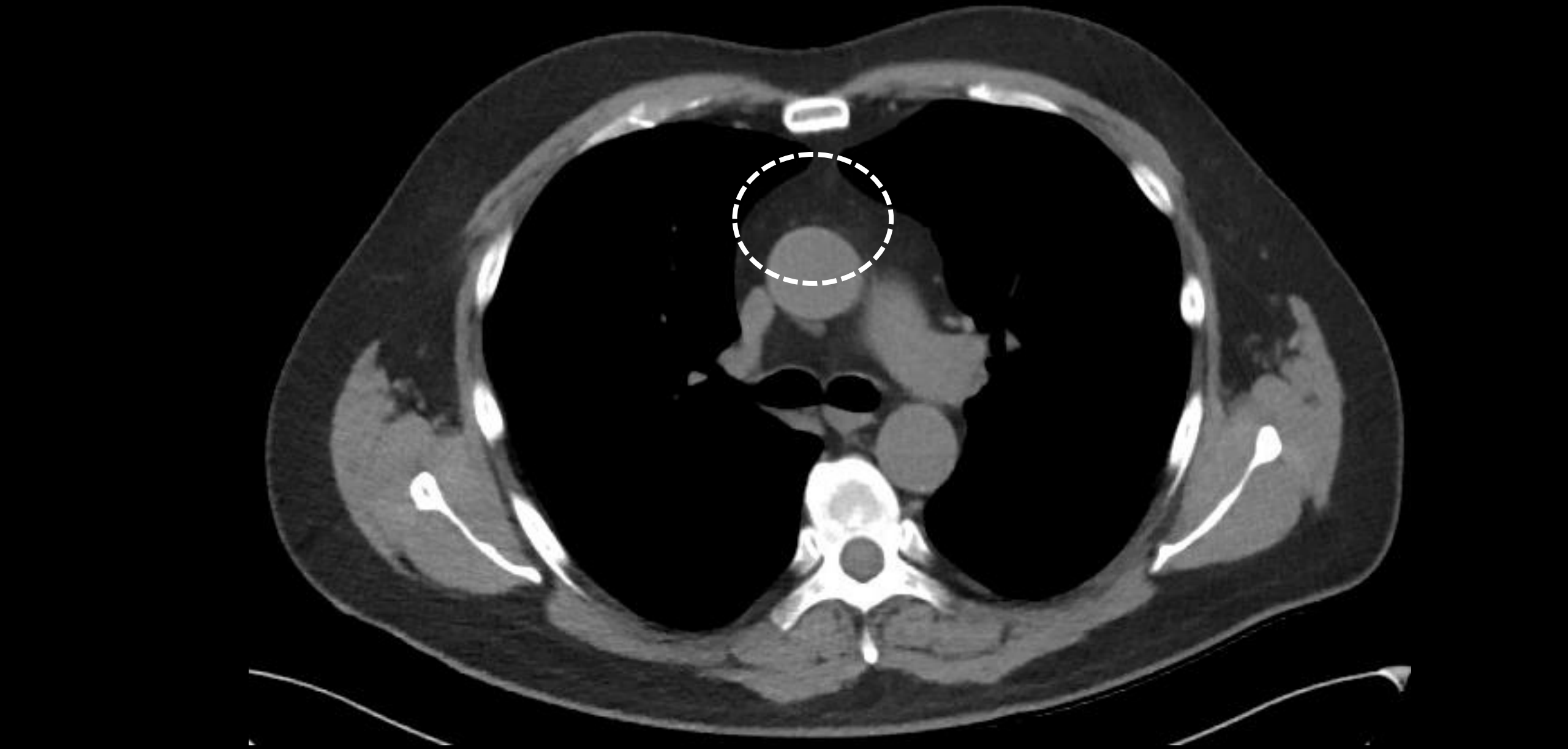
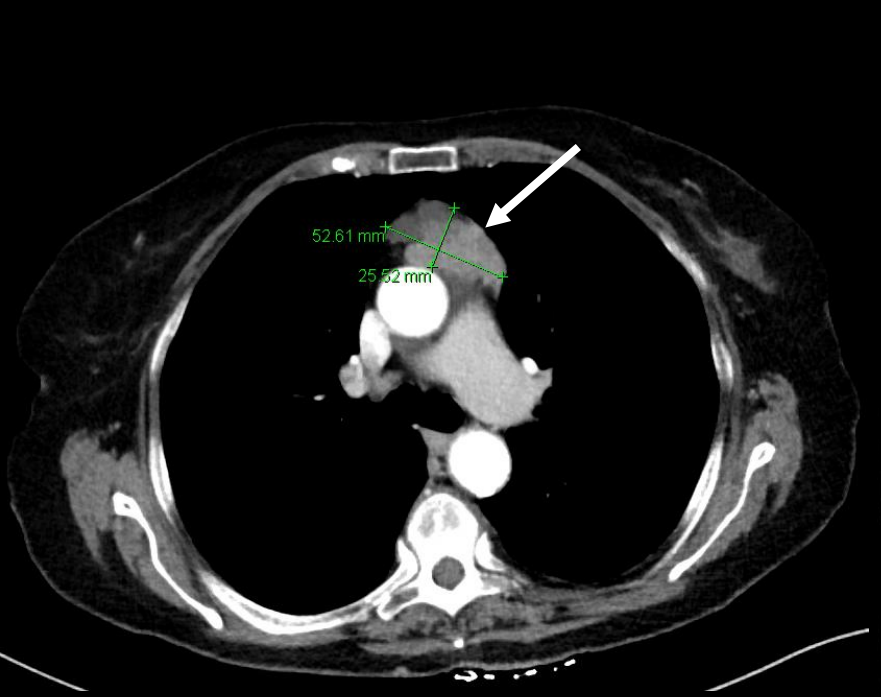
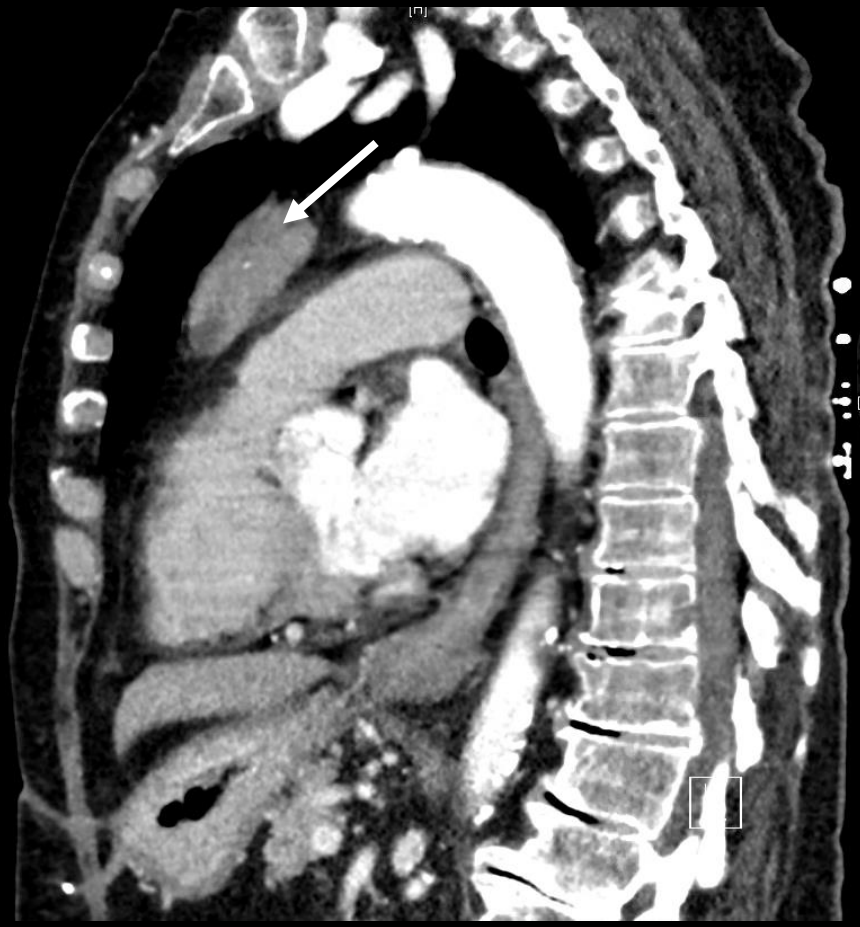
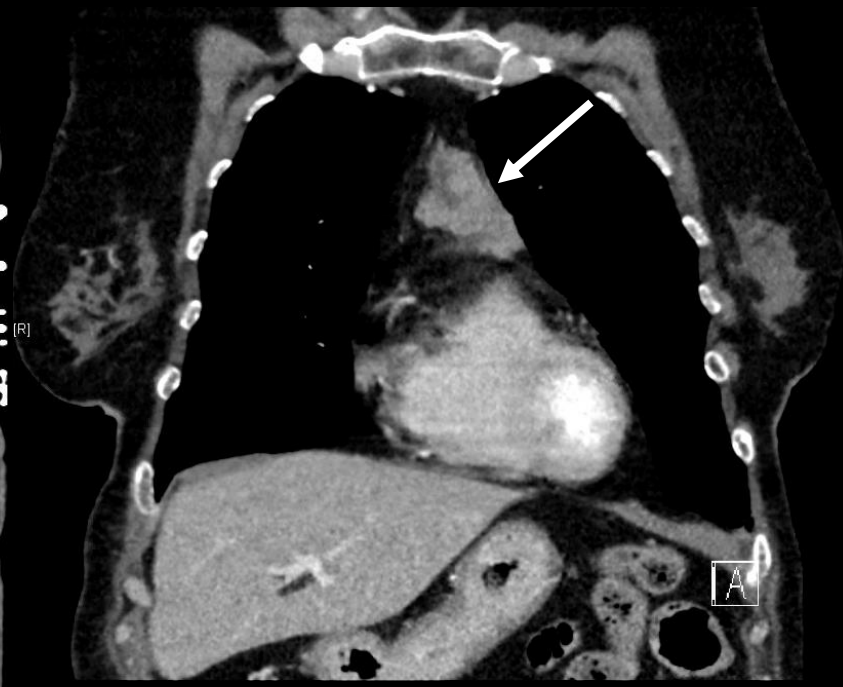


Patient, no thymoma







Thymomatous MG

Part II: Diagnosis of MG

MG diagnosis

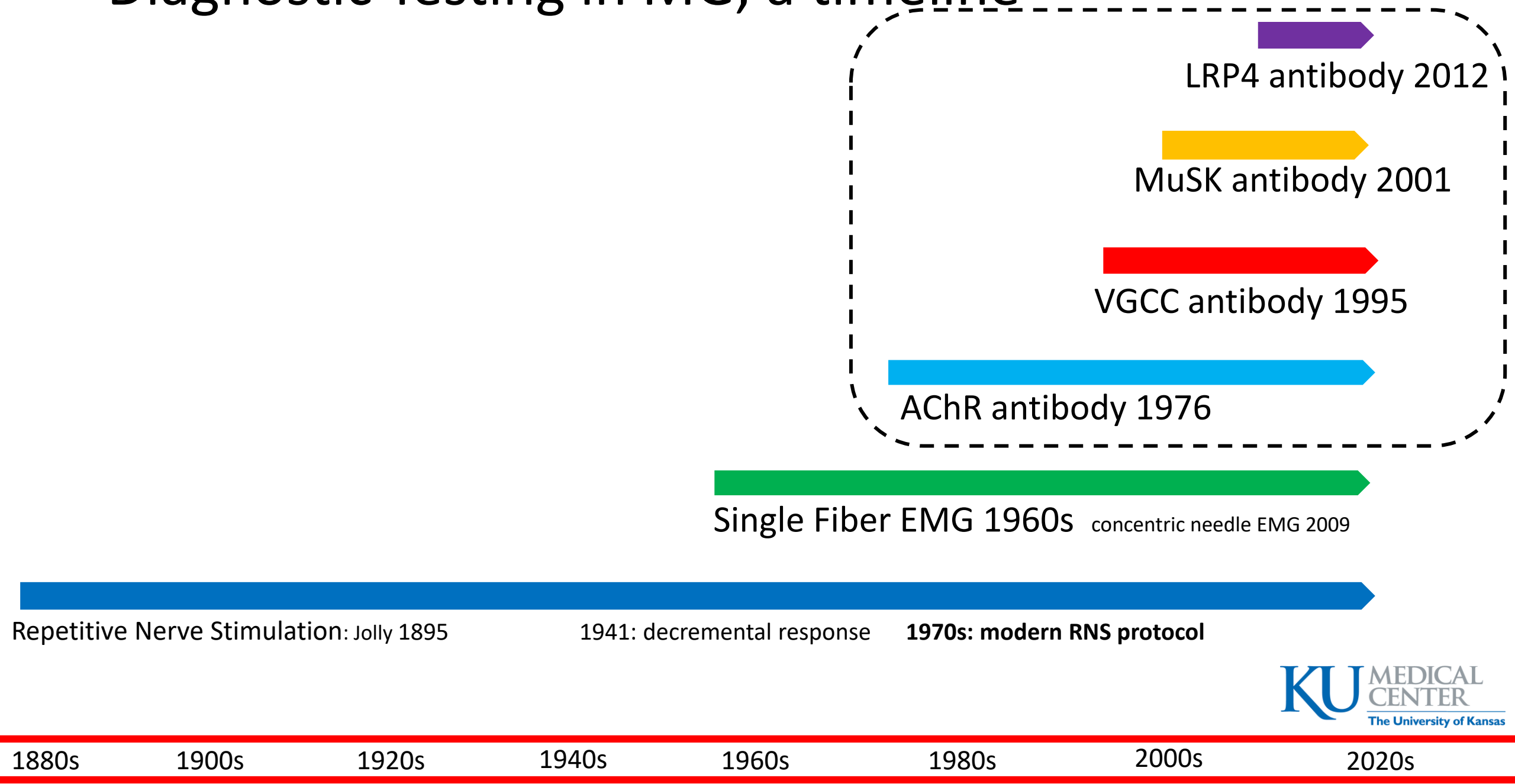
- Clinical history often can be quite specific

Ocular Symptoms • double vision or droopy eyelids, **asymmetric**	**65%**
Bulbar Weakness • slurred speech • voice changes (soft, nasal) • difficulty chewing or swallowing	**<25%**
Limb Weakness, mostly symmetric	**14%-27%**

- The neurologic examination can also show many characteristic findings

The Rational Clinical Examination

Diagnostic Testing in MG, a timeline



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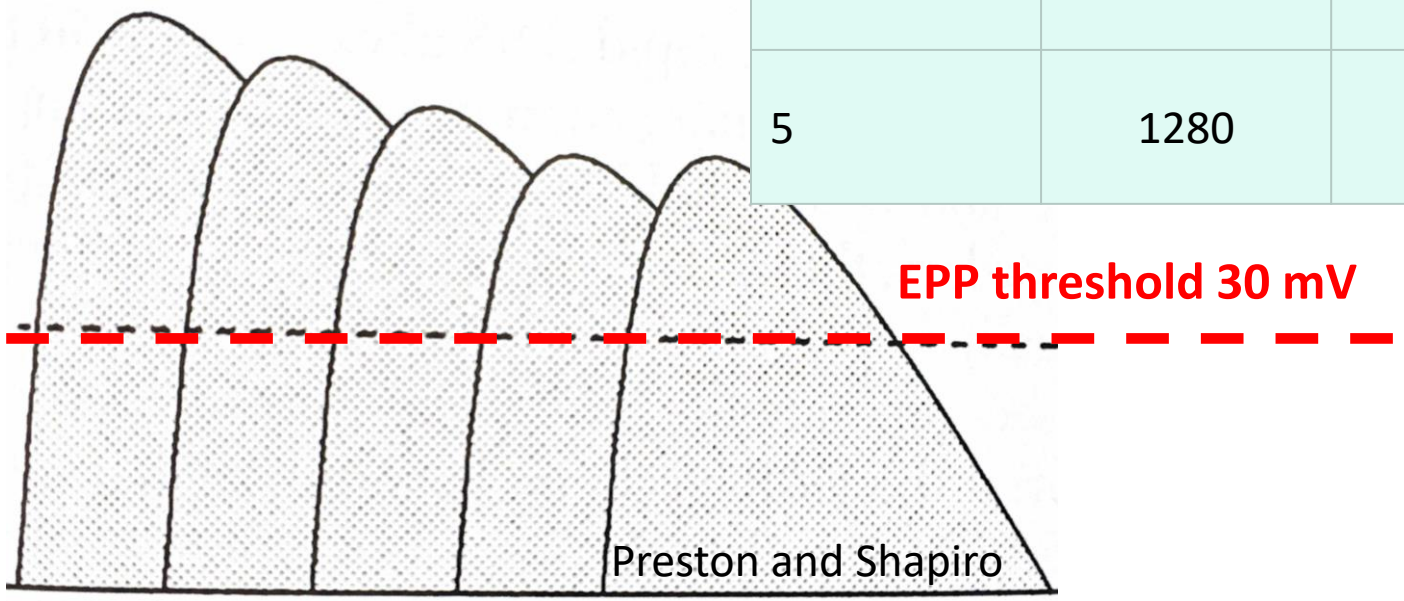
MG diagnosis

- Seronegative cases, reliant on careful examination and electrodiagnostic testing

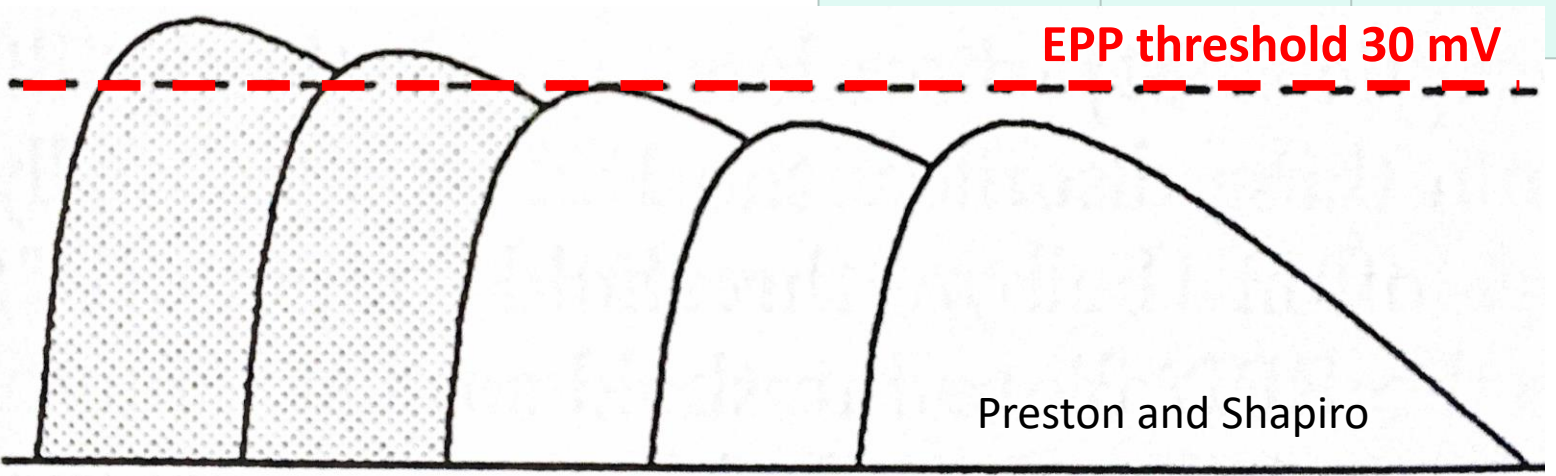
Model for understanding neuromuscular transmission: NORMAL (3Hz stimuli)

Stimulus	ACh Quanta available for release	ACh quanta released in synapse (*20% of total*)	Endplate potential (5 ACh quanta = 1 mv)	muscle fiber action potential	CMAP / symptoms
1	2000	400	80	+	Normal/No weakness
2	1600	320	64	+	Normal/No weakness
3	1280	256	52	+	Normal/No weakness
4	1024	204	40	+	Normal/No weakness
5	1280	256	52	+	Normal/No weakness



Model for understanding postsynaptic neuromuscular transmission deficit: MG (3Hz stimuli)

Stimulus	ACh Quanta available for release	ACh quanta released in synapse (*20% of total*)	Endplate potential (10 ACh quanta = 1 mv)	muscle fiber action potential	CMAP / symptoms
1	2000	400	40	+	Normal
2	1600	320	32	+	Normal
3	1280	256	26	–	Decrement & weakness
4	1024	204	20	–	Decrement & weakness
5	1280	256	26	–	Decrement & weakness



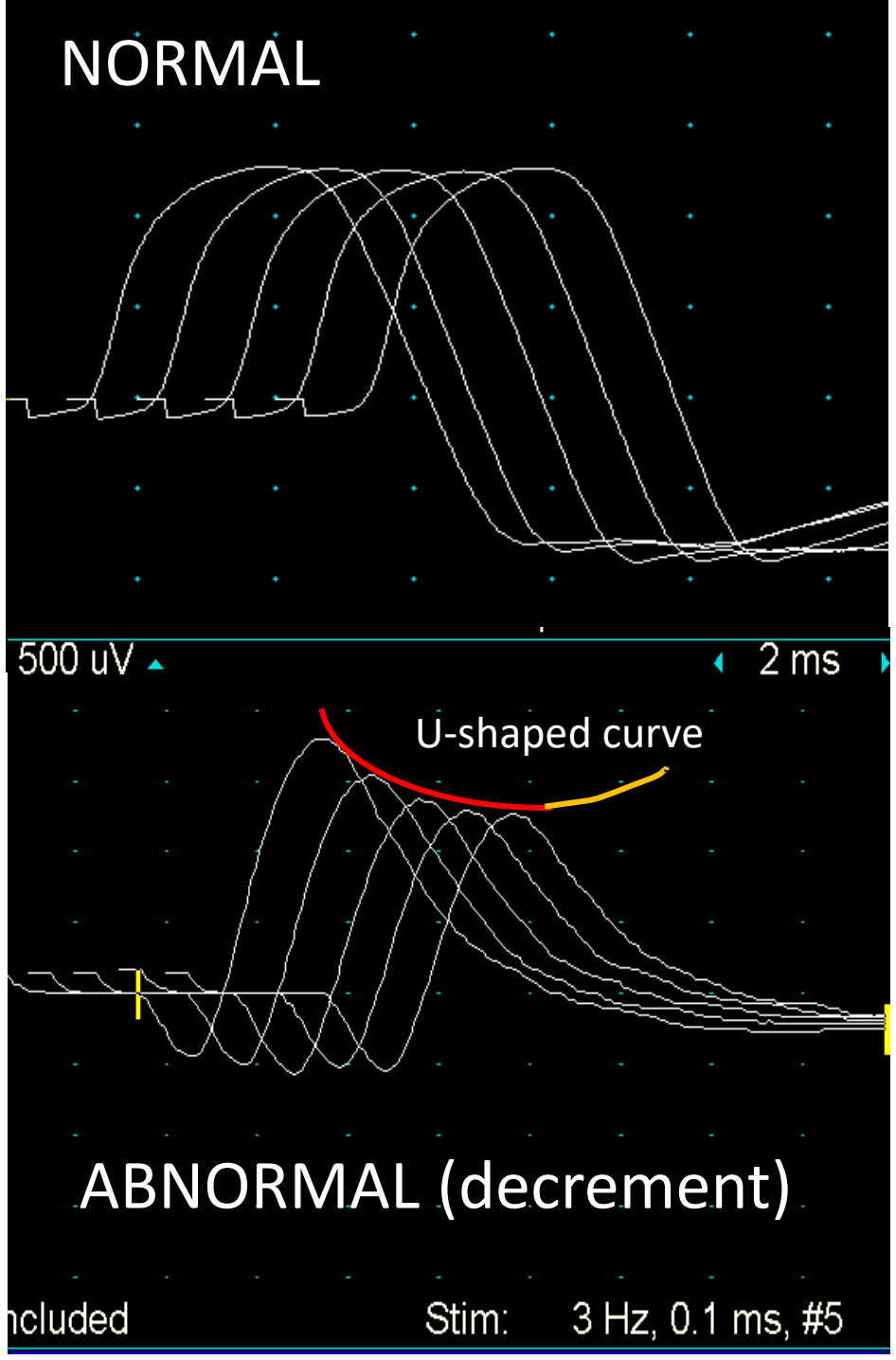
Repetitive Nerve Stimulation

- Motor nerve conductions, but do repetitive nerve stimulation
- Frequency: 3 Hz
- Artifact is frequent

Normal: stable amplitudes

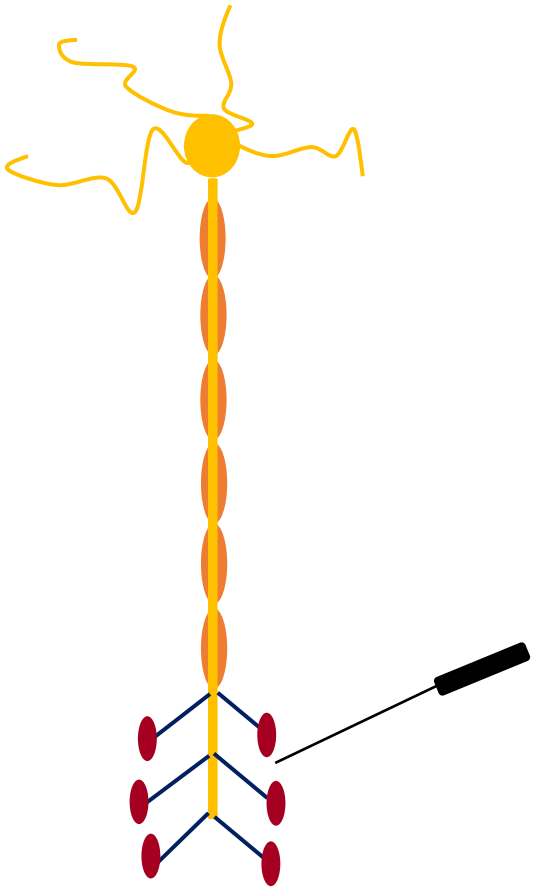
Myasthenia gravis

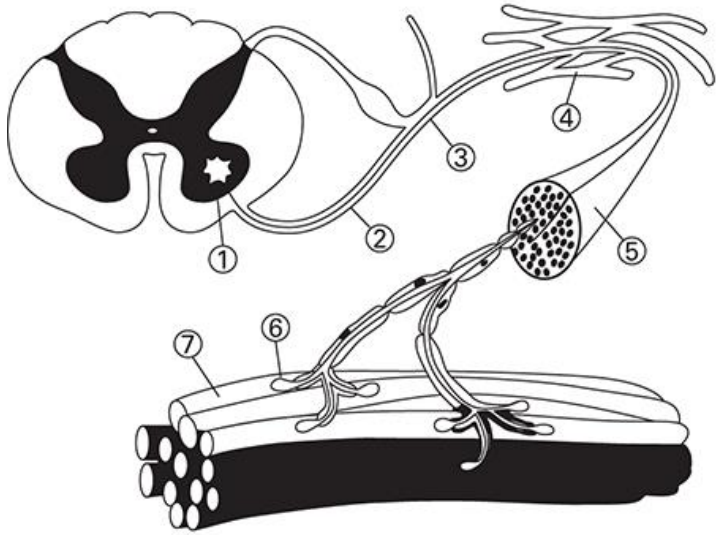
- Amplitude decrement of 10% is considered abnormal
- Biggest decline between first and second CMAPs
- Lowest amplitude in 4th response
- U-shaped appearance
- **Must be reproducible**



When do you do single fiber EMG?

Single fiber EMG





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2. Nerve root
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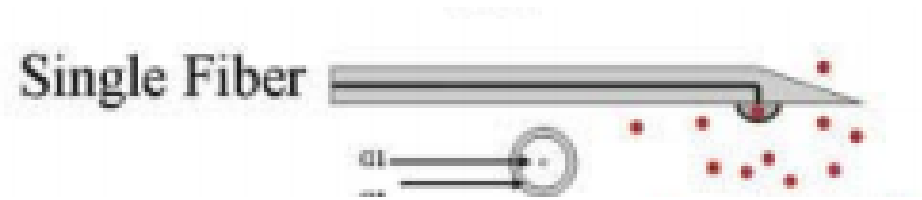

FIGURE 2. Electrode types used in recording electromyographic signals. The recording areas of each electrode type are shown by the hashed regions.

0.0005 mm^2

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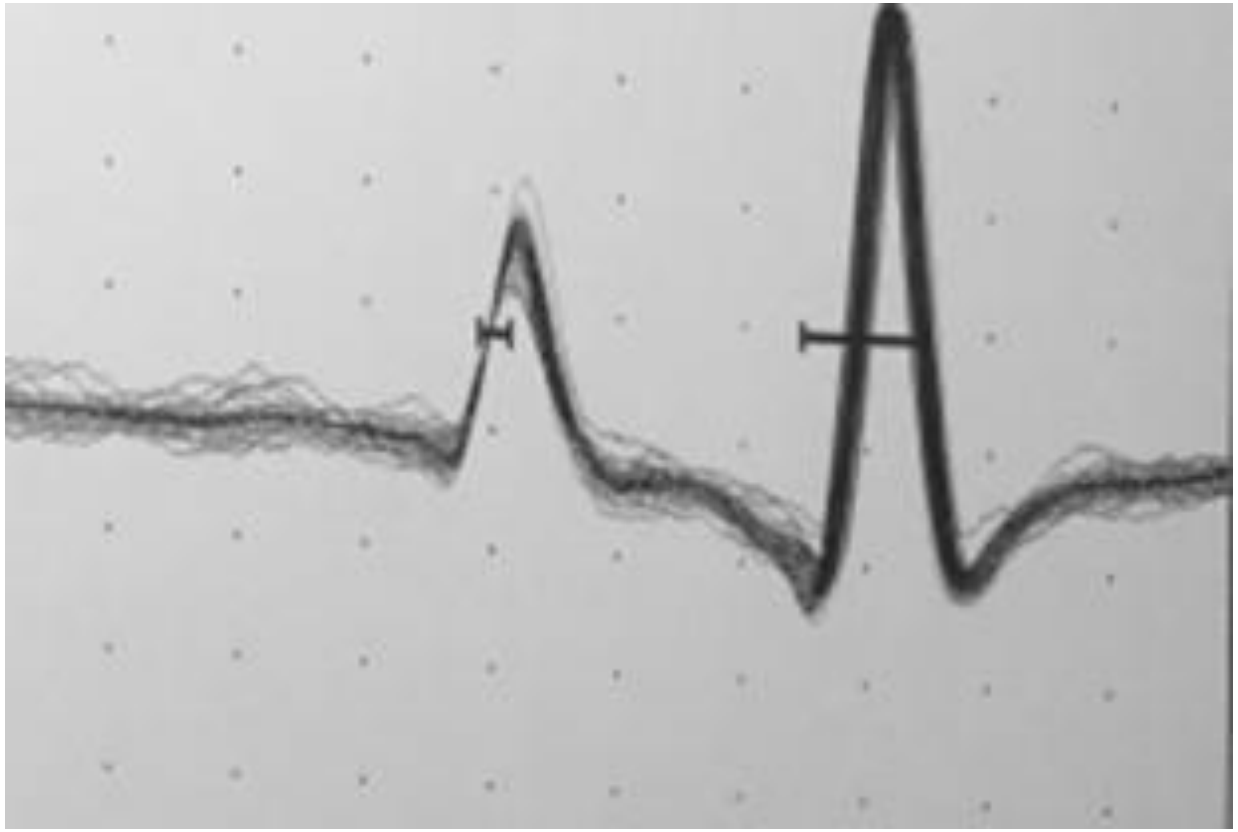
- Variability of the interpotential interval is a property of a pair of muscle fibers and is known as jitter
- 2 time locked potentials, first potential is the trigger

$$\text{MCD} = \frac{|IPI_1 - IPI_2| + |IPI_2 - IPI_3| + \cdots + |IPI_{n-1} - IPI_n|}{n - 1}$$



Normal jitter values, superimposed traces

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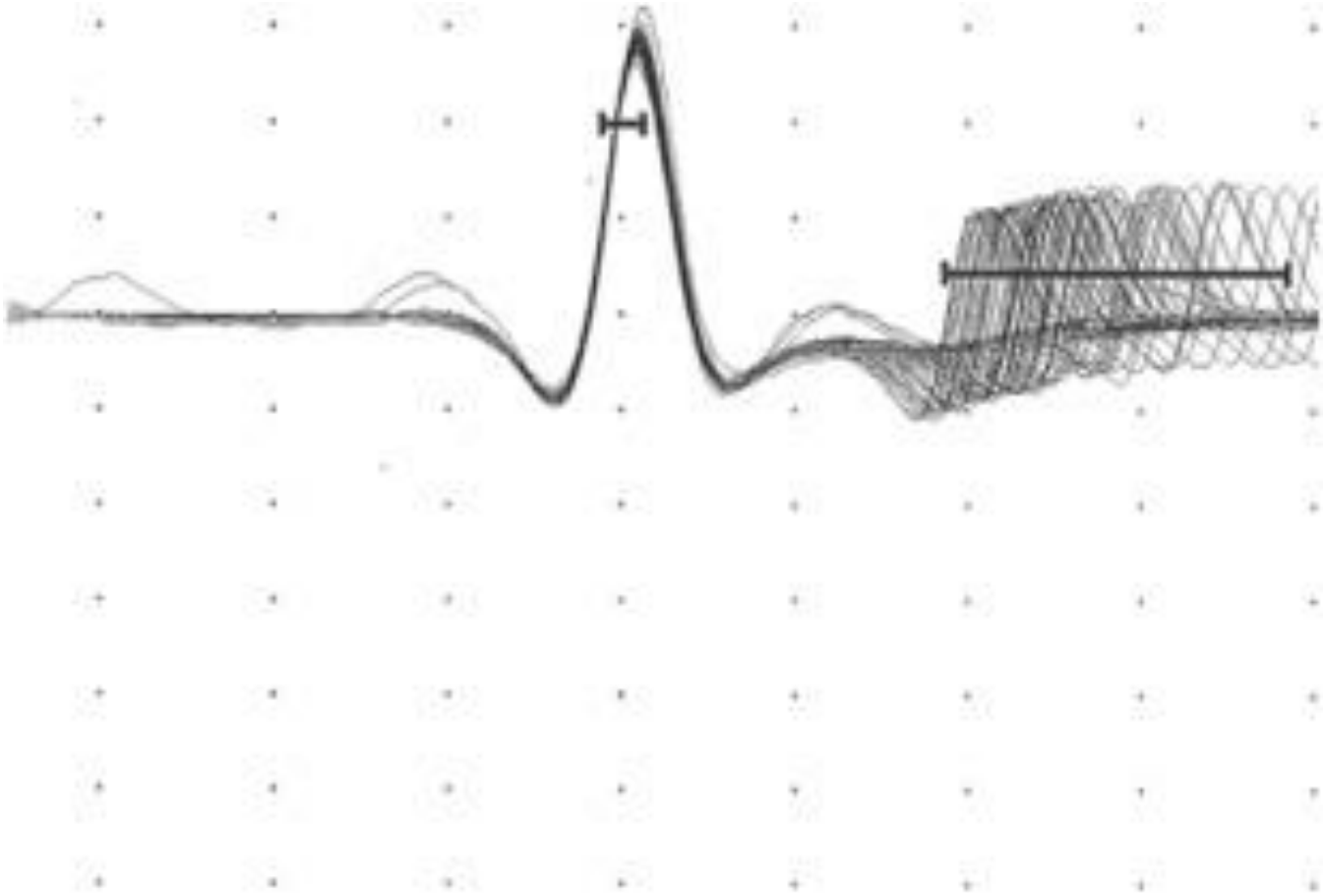
Increased Jitter

- Jitter is increased when reaching the threshold potential is harder, as in MG, LEMS but also diseases like ALS and myopathies



Abnormal jitter values, superimposed traces

Single Fiber EMG

- Very sensitive, but not specific
- Test often obtained at specialized centers (limited availability)
- If jitter is normal in a weak muscle, the patient does not have a NMJ disorder

Sensitivity of Diagnostic testing in MG

	Ocular MG	Generalized MG
AChR antibodies	40-50%	80-90%
MuSK antibodies (in AChR ab seronegative pts)	<10%	40-50%
LRP4 antibodies (in AChR and MuSK double senegative pts)	10%	10%
Repetitive nerve stimulation	15-45%	75-80%
SFEMG	80-95%	>92%

Dr. Pleitez, Houston, TX

- Treatment and future directions

Therapy timeline in MG

Dr. Mary Walker, 1920s

Eculizumab (FDA 2017)

Rituximab

IVIG

SCIG

Steroid sparring immunosuppressants: AZA, CCL, TRO, MMF, MTX, CCP

Plasma exchange

Corticosteroids

Thymectomy

Thoracoscopy

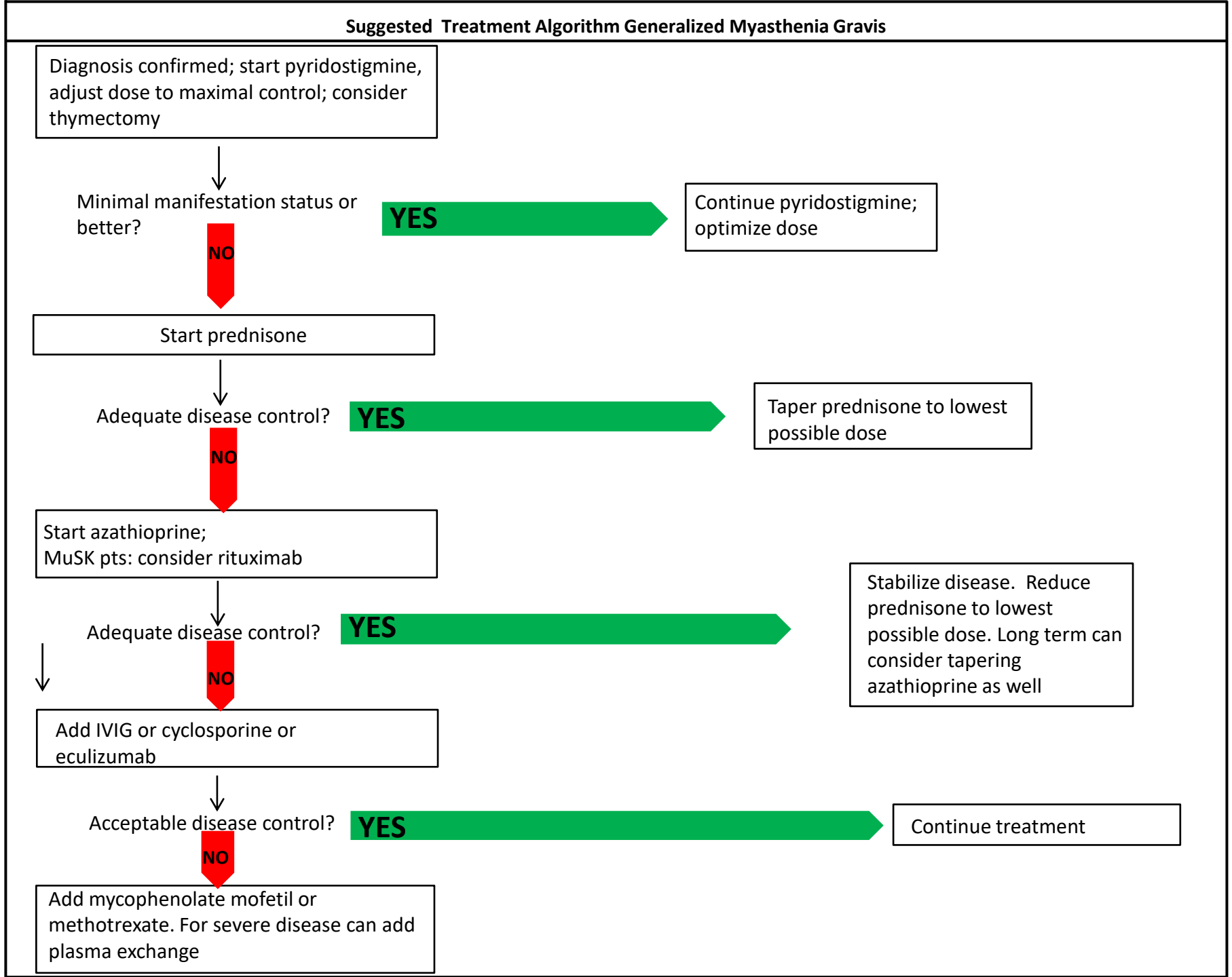
Robotic techniques introduced

MGTX trial

AChE-I: physostigmine, neostigmine, pyridostigmine 1955 (FDA)

Mechanical ventilation

1934 1940s 1950s 1960s 1970s 1980s 1990s 2000s 2010s 2020s



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MANAGEMENT OF AUTOIMMUNE MYASTHENIA GRAVIS AND FUTURE DIRECTIONS

MILVIA Y. PLEITEZ, MD

BAYLOR COLLEGE OF MEDICINE

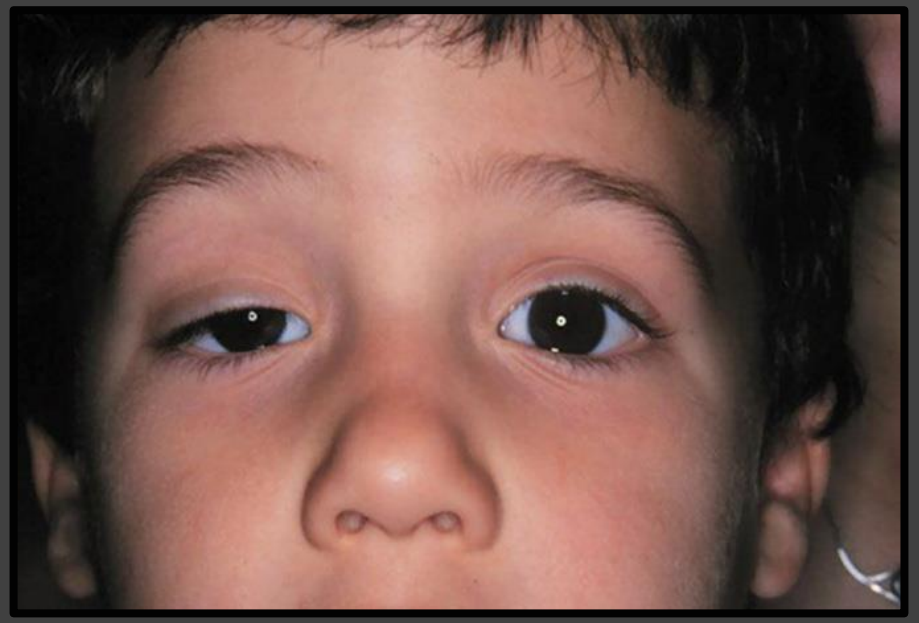
Baylor College of Medicine

MYASTHENIA GRAVIS TYPES

Neonatal- transient

https://healthhearty.com/myasthenia-gravis-symptoms-in-children

Juvenile



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MYASTHENIA GRAVIS TYPES

OCULAR

MYASTHENIA GRAVIS TYPES

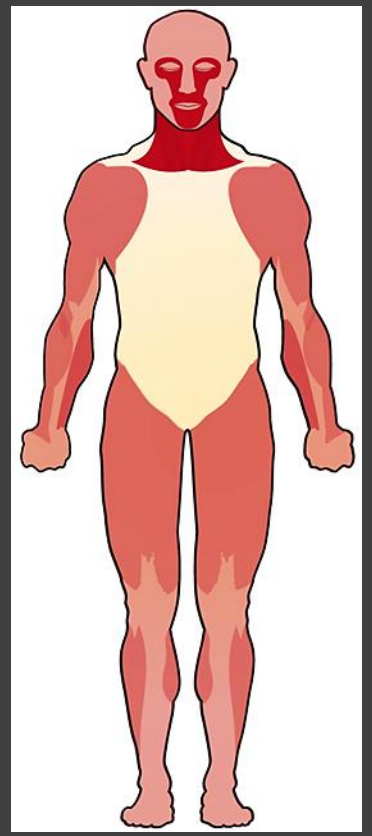
Generalized

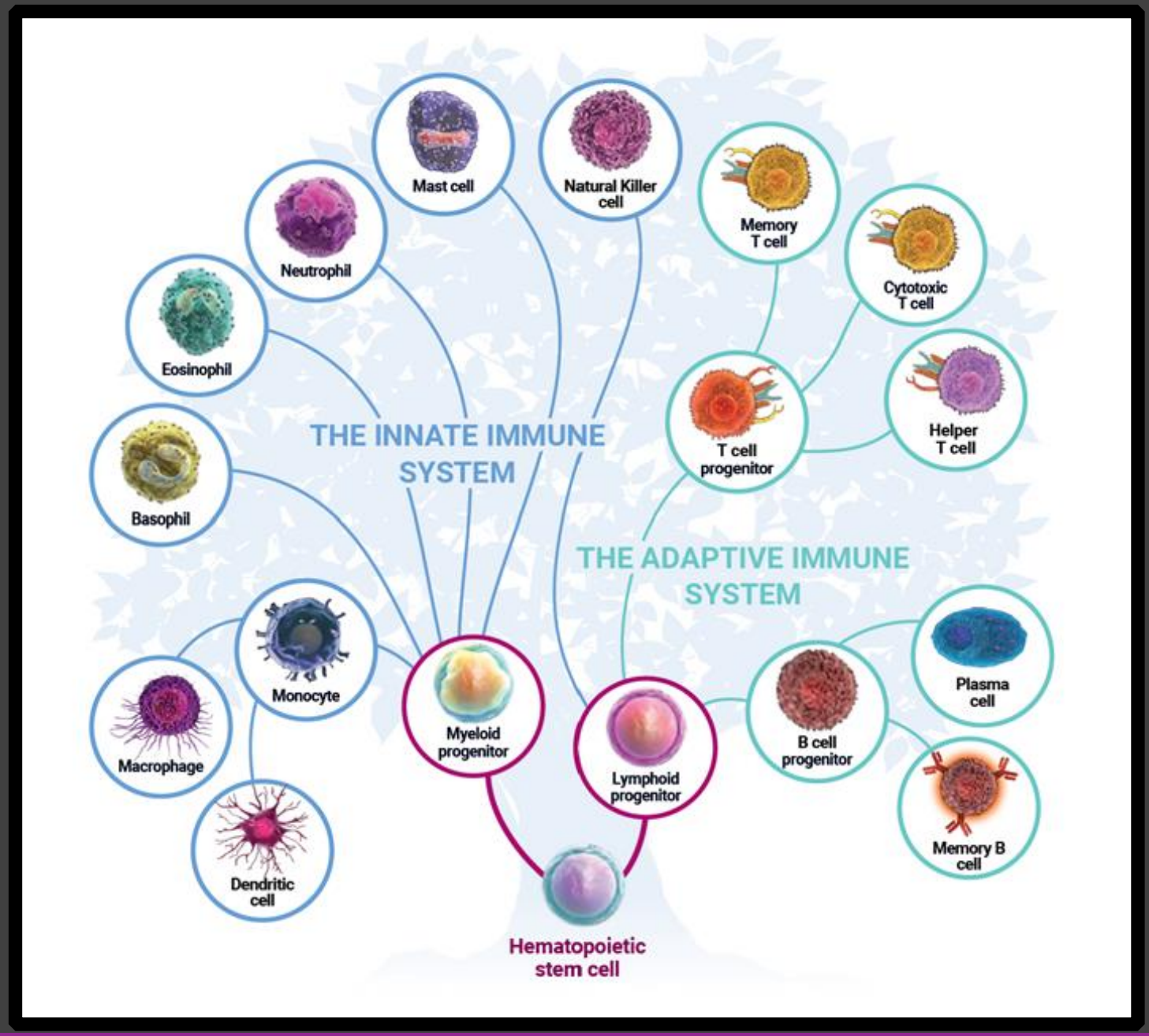
AChR abs

MuSK abs

Double SeroNegative:

- LRP4 abs
- Others




Mast cell
Natural Killer cell
Neutrophil
Memory T cell
Cytotoxic T cell
Eosinophil
Helper T cell
T cell progenitor
Basophil
THE INNATE IMMUNE SYSTEM
THE ADAPTIVE IMMUNE SYSTEM
Monocyte
Plasma cell
Macrophage
Myeloid progenitor
Lymphoid progenitor
B cell progenitor
Memory B cell
Dendritic cell
Hematopoietic stem cell

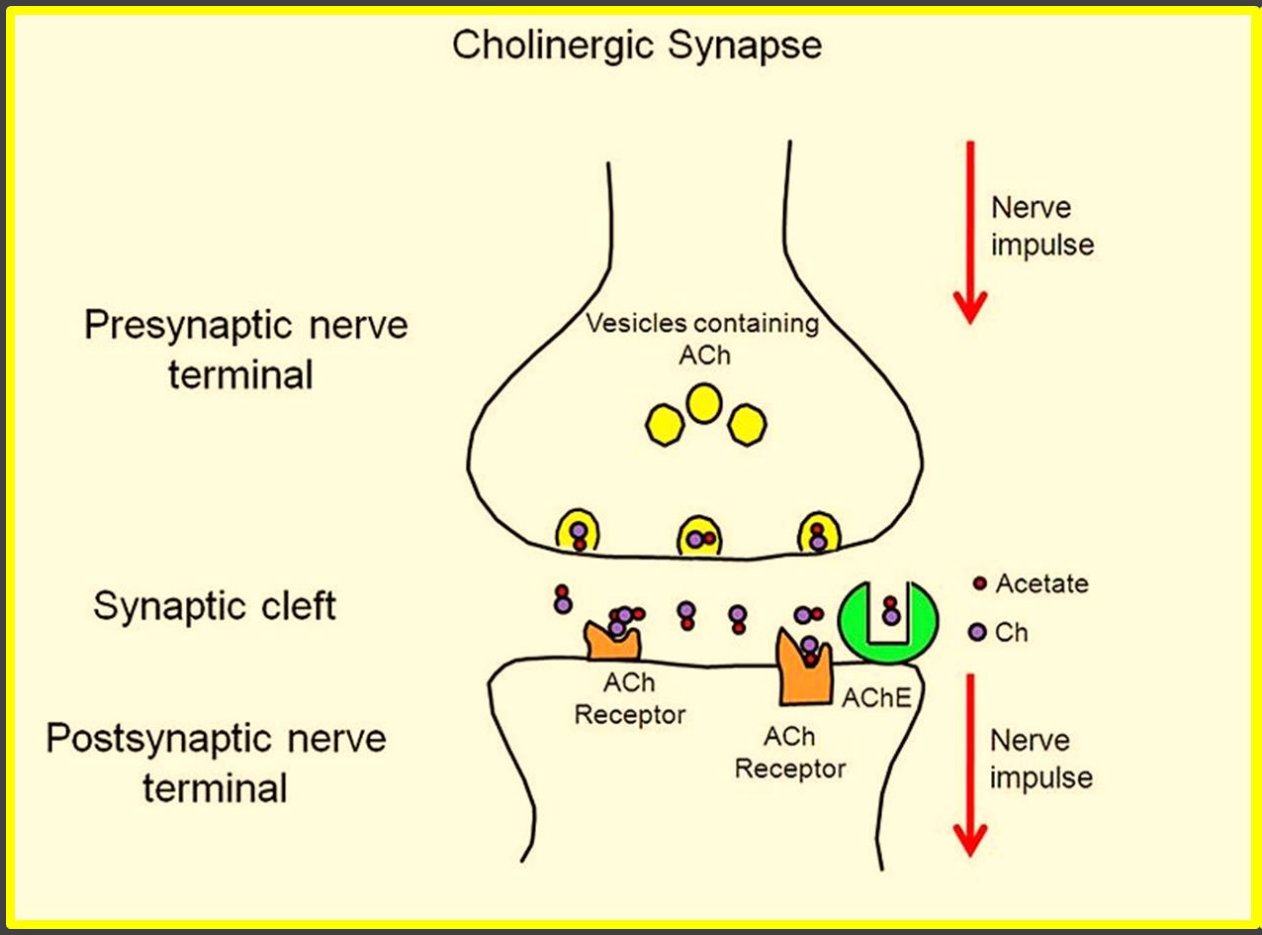
MEDICATIONS FOR OCULAR MG

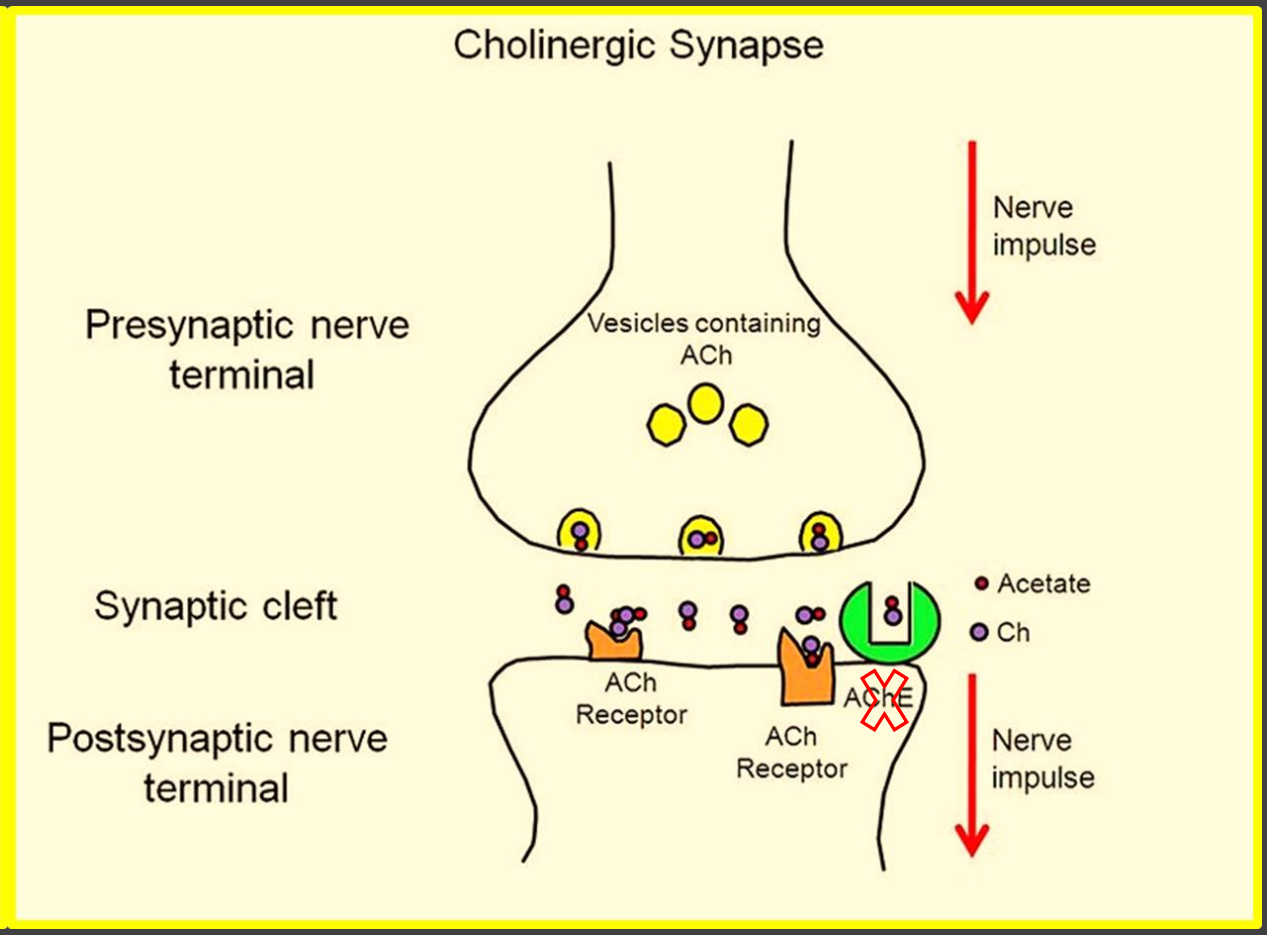
SYMPTOMATIC

- *CHOLINESTERASE INHIBITORS*
  - PYRIDOSTIGMINE BROMIDE (MESTINON)
  - NEOSTIGMINE (PROSTIGMIN)
- *LID CRUTCHES*
- *EYELID/EYE MUSCLE SURGERY*

DISEASE TREATING

- *CORTICOSTEROIDS*
  - PREDNISONE
  - HYDROCORTISONE
- *STEROID SPARING MEDICATIONS*
  - *AZATHIOPRINE (IMURAN)*
  - *MYCOPHENOLATE MOFETIL(CELLCEPT)*
  - *CYCLOSPORINE A (SANDIMMUNE, NEORAL)*
- *OTHERS*
  - *IVIG*





Pyridostigmine Bromide
(Mestinon)

MEDICATIONS FOR OCULAR MG

SYMPTOMATIC

- *CHOLINESTERASE INHIBITORS*
  - PYRIDOSTIGMINE BROMIDE (MESTINON)
  - NEOSTIGMINE (PROSTIGMIN)
- *LID CRUTCHES*
- *EYELID/EYE MUSCLE SURGERY*

DISEASE TREATING

- *CORTICOSTEROIDS*
  - PREDNISONE
  - HYDROCORTISONE
- *STEROID SPARING MEDICATIONS*
  - *AZATHIOPRINE (IMURAN)*
  - *MYCOPHENOLATE MOFETIL(CELLCEPT)*
  - *CYCLOSPORINE A (SANDIMMUNE, NEORAL)*
- *OTHERS*
  - *IVIG*

MEDICATIONS FOR GENERALIZED MG

SYMPTOMATIC

- *CHOLINESTERASE INHIBITORS*
  - PYRIDOSTIGMINE BROMIDE (MESTINON)
  - NEOSTIGMINE (PROSTIGMIN)

DISEASE TREATING

- *CORTICOSTEROIDS*
  - PREDNISONE
  - HYDROCORTISONE

MEDICATIONS FOR GENERALIZED MG

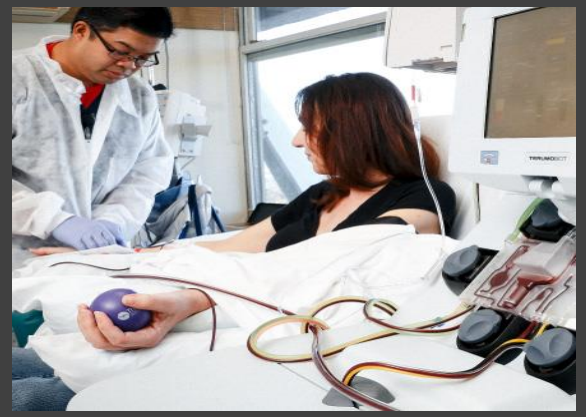
DISEASE TREATING

- STEROID SPARING MEDICATIONS/OTHER IMMUNOSUPPRESSANTS
  - AZATHIOPRINE (IMURAN)
  - MYCOPHENOLATE MOFETIL(CELLCEPT)
  - CYCLOSPORINE A (SANDIMMUNE, NEORAL)
  - RITUXIMAB (RITUXAN)
  - ECULIZUMAB (SOLIRIS)
  - CYCLOPHOSPHAMIDE (CYTOXAN)
  - METHOTREXATE

MEDICATIONS FOR GENERALIZED MG

DISEASE TREATING

- OTHER IMMUNOTHERAPIES
  - IMMUNOGLOBULIN
    - IV
    - SQ
  - PLASMA EXCHANGE
    - PERIPHERAL ACCESS
    - CENTRAL LINE
    - AVF



MuSK MYASTHENIA GRAVIS TREATMENTS

- MESTINON
- PREDNISONE
- RITUXIMAB
- AZATHIOPRINE/CELLCEPT/CYCLOSPORINE
- PLASMA EXCHANGE

MG TREATMENT

ACUTE:

- MESTINON
- PREDNISONE OR OTHER CORTICOSTEROIDS
- IVIgG
- THERAPEUTIC PLASMAPHORESIS

MG TREATMENT

CHRONIC:

- MESTINON
- CORTICOSTEROIDS
- IVIgG
- THERAPEURIC PLASMAPHORESIS

MG TREATMENT

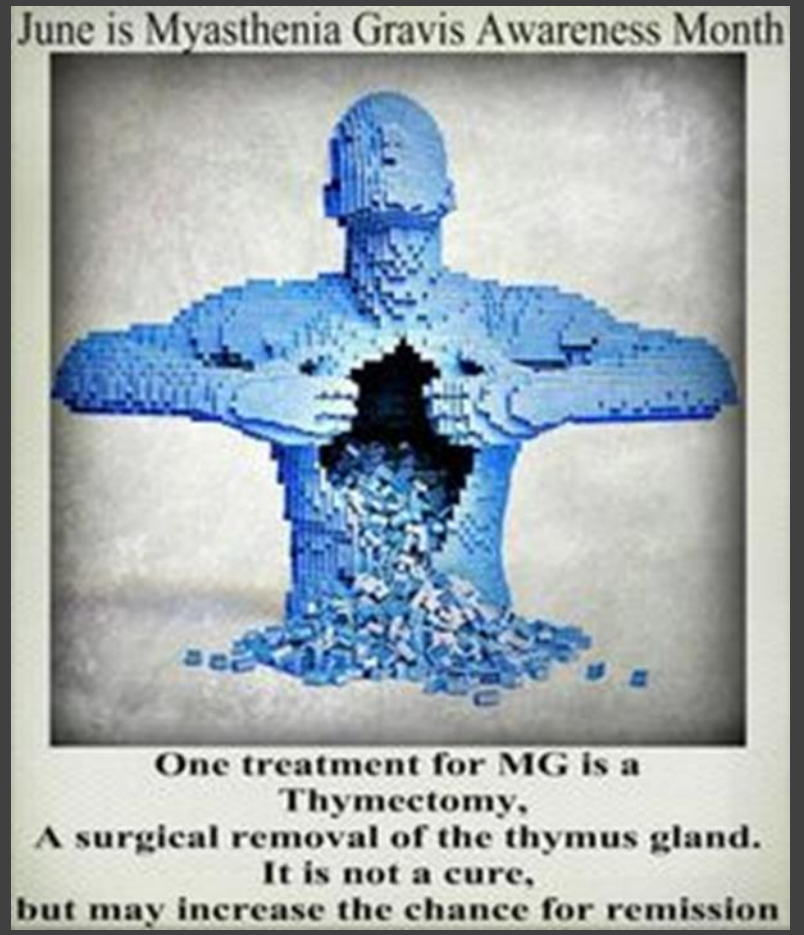
CHRONIC:

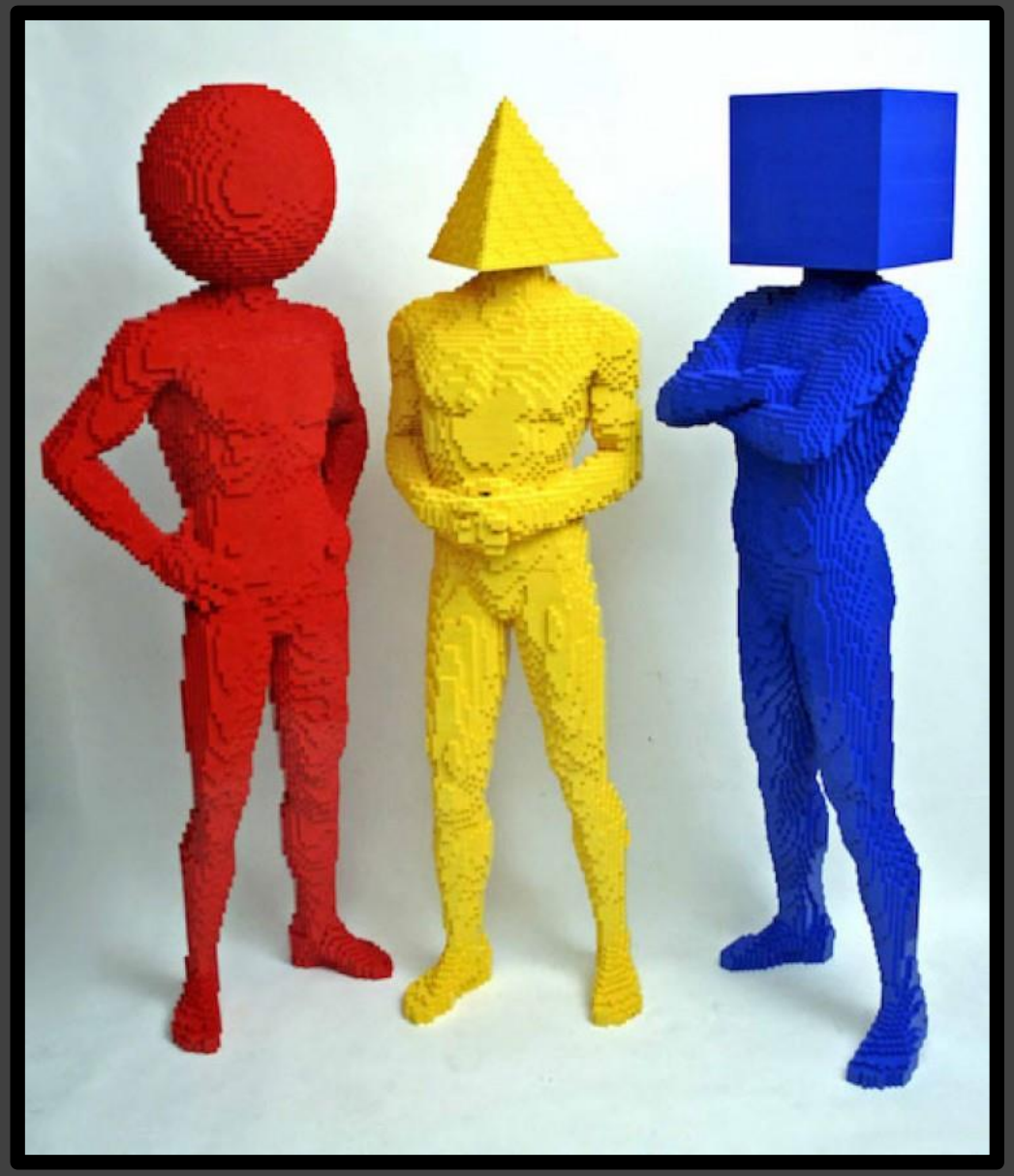
- *AZATHIOPRINE (IMURAN)*
- *MYCOPHENOLATE MOFETIL(CELLCEPT)*
- *CYCLOSPORINE A (SANDIMMUNE, NEORAL)*
- *RITUXIMAB (RITUXAN)*
- *ECULIZUMAB (SOLIRIS)*
- *CYCLOPHOSPHAMIDE (CYTOXAN)*
- *METHOTREXATE*

MEDICATIONS FOR GENERALIZED MG

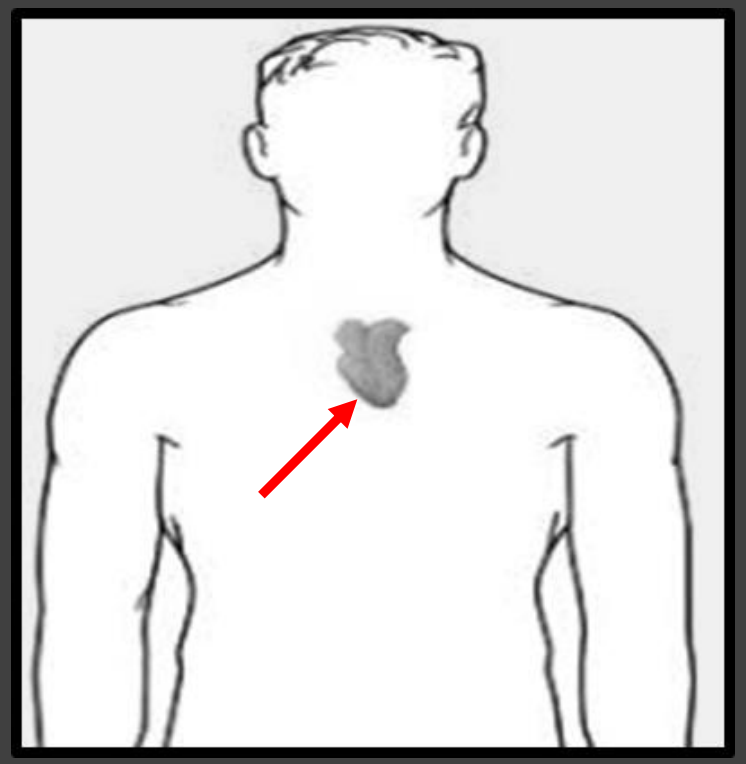
DISEASE TREATING

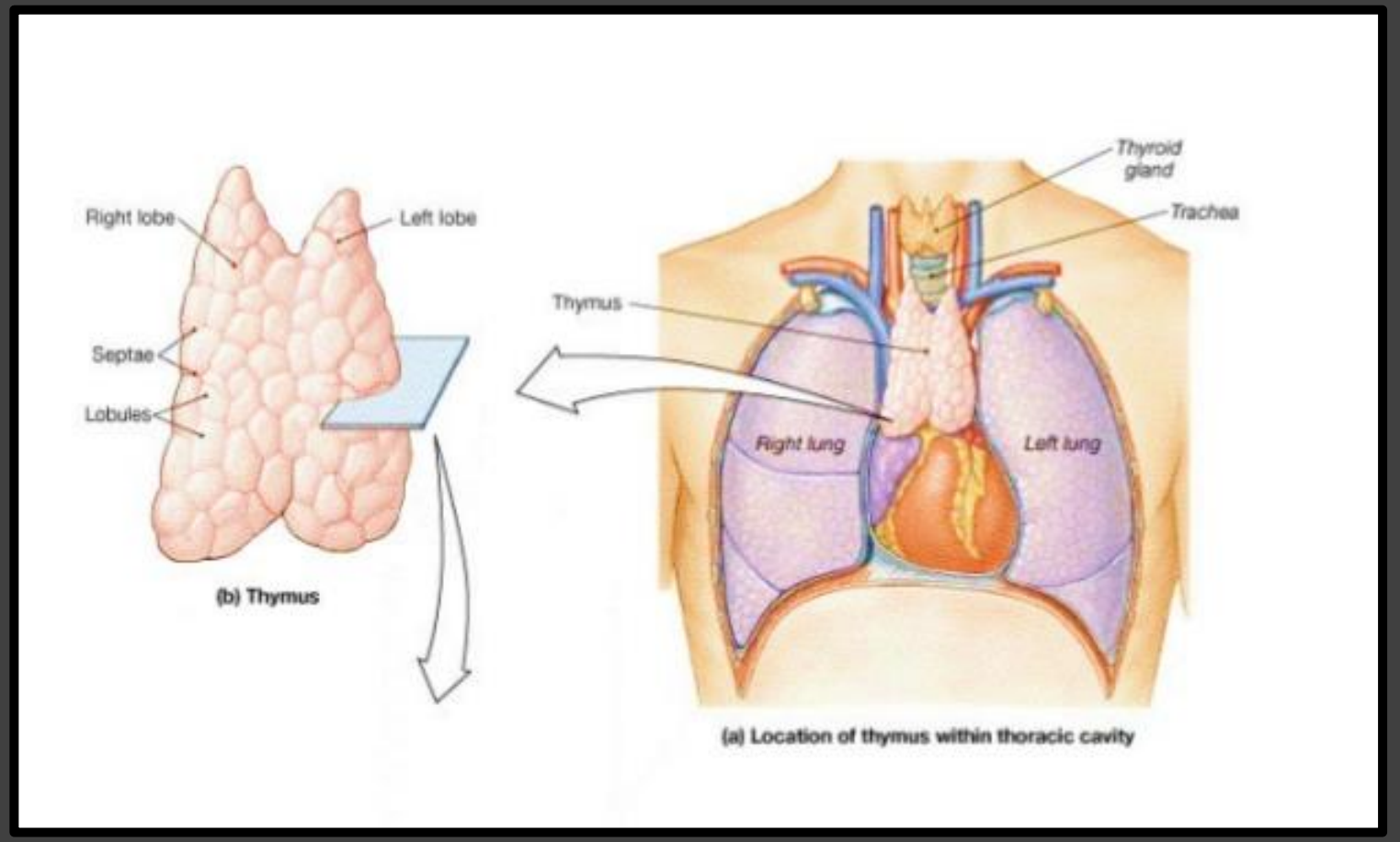
- ***THYMECTOMY***
  - ***THYMOMA***
  - ***AChR AB POSITIVE***
  - ***REFRACTORY MG EVEN IF SERONEAGTIVE***





THYMUS GLAND





WHAT IS THE THYMUS GLAND?

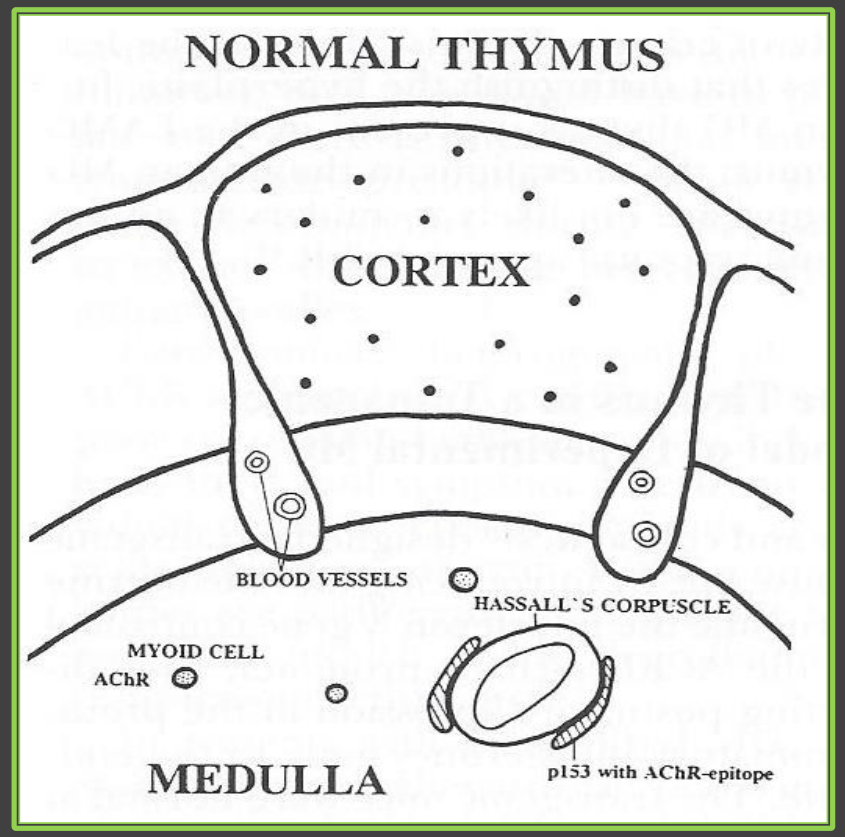
- SPECIALIZED PART OF THE IMMUNE SYSTEM THAT HELPS PROPAGATE MYASTHENIA GRAVIS
- PRINCIPAL ORGAN THAT “RAISES, NURTURES & DEVELOPS” A SPECIFIC PART OF THE IMMUNE SYSTEM KNOWN AS “T-CELLS”
- TEACHES THE IMMUNE SYSTEM TO RECOGNIZE FOREIGN BODIES
- NEEDED DURING INFANCY/CHILDHOOD TO BUILD UP IMMUNE SYSTEM
- INVOLUTES OR GETS SMALLER AND LESS FUNCTIONAL AS YOU GET OLDER

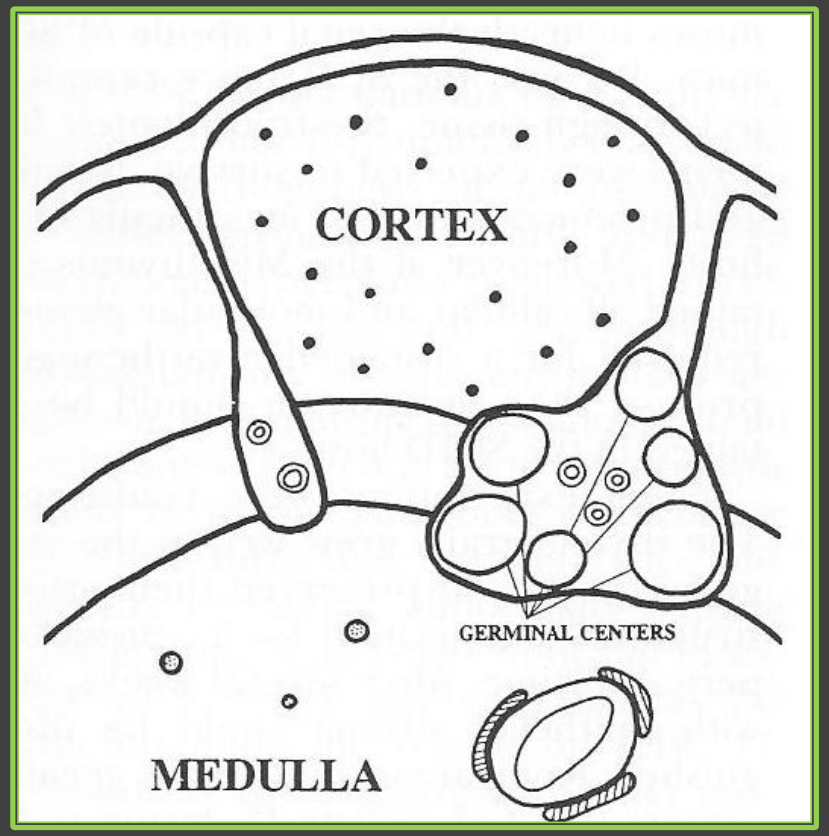
MG THYMUS

80% PATIENTS WITH GENERALIZED MG & POSITIVE ACETYLCHOLINE RECPTOR Abs HAVE ABNORMAL THYMUS GLANDS:

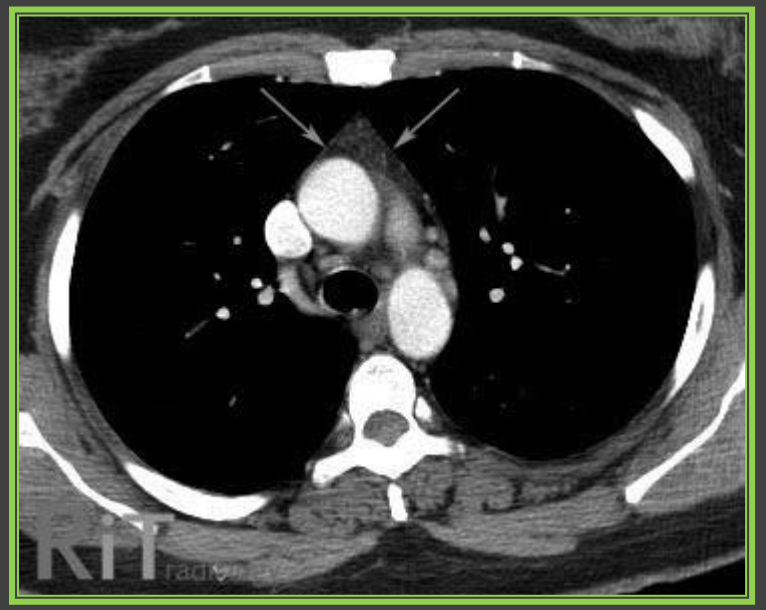
- THYMIC HYPERPLASIA ≈70%
- THYMOMA ≈15%
- THYMIC INVOLUTION

ROLE OF THYMUS IN PATIENTS WHO DO NOT HAVE ACETYLCHOLINE Abs OR WHO HAVE MuSK Abs IS UNCLEAR

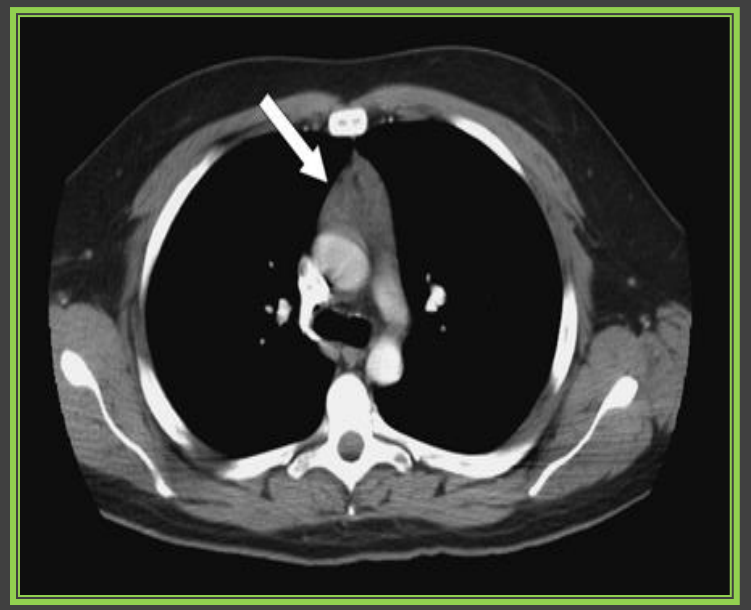




HYPERPLASTIC THYMUS

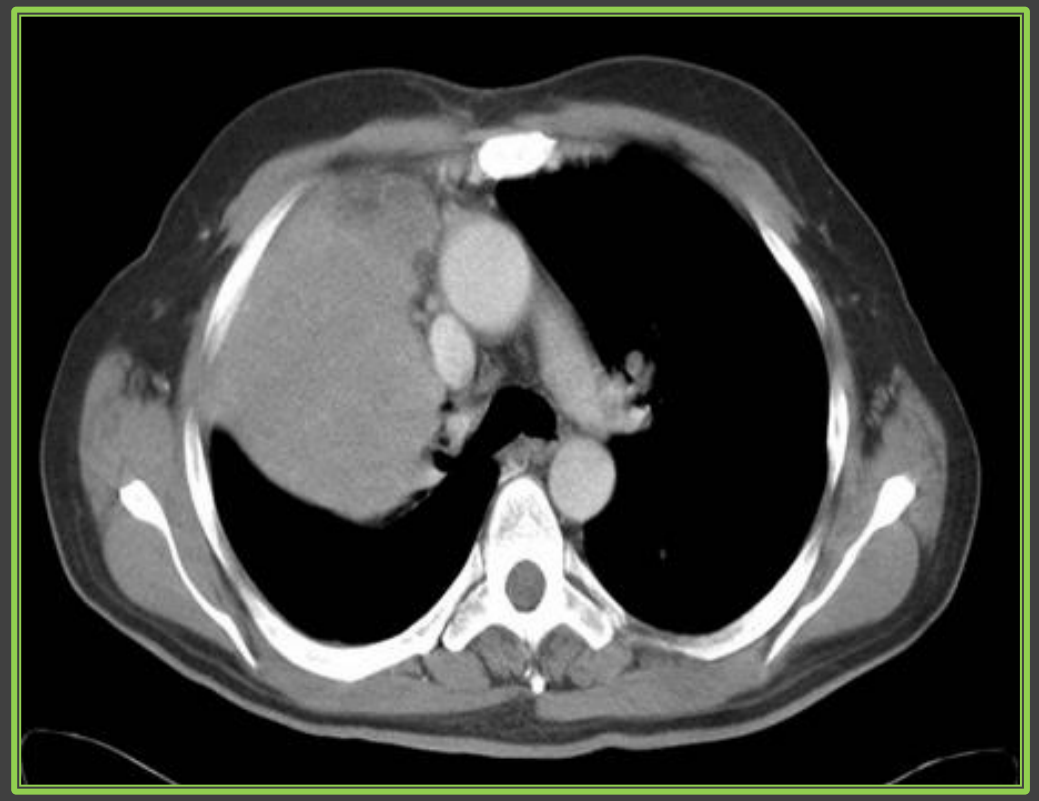


NORMAL THYMUS



THYMIC HYPERPLASIA

THYMOMA



FACTORS THAT AGGRAVATE MYASTHENIA GRAVIS

STRESS/ANXIETY

SLEEP DEPRIVATION

MEDICAL ILLNESSES

HEAT/HUMIDITY

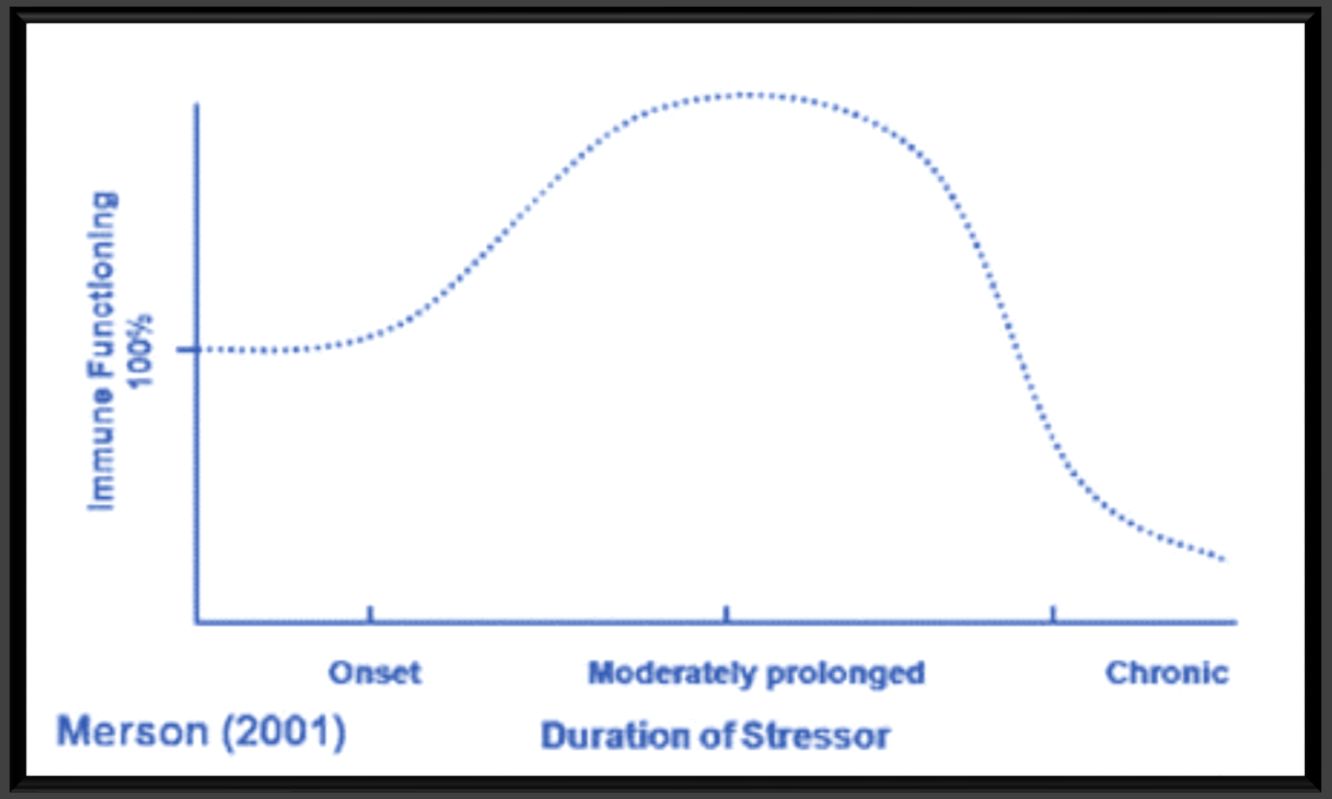
MENSES

MEDICINE COMPLIANCE

EXERCISING INCORRECTLY

MEDICATIONS

IMMUNE FUNCTION AND STRESS



STRESS RELIEVERS

Get active

Eat a healthy diet

Avoid too much caffeine, alcohol, tobacco.

Meditate

Connect with others

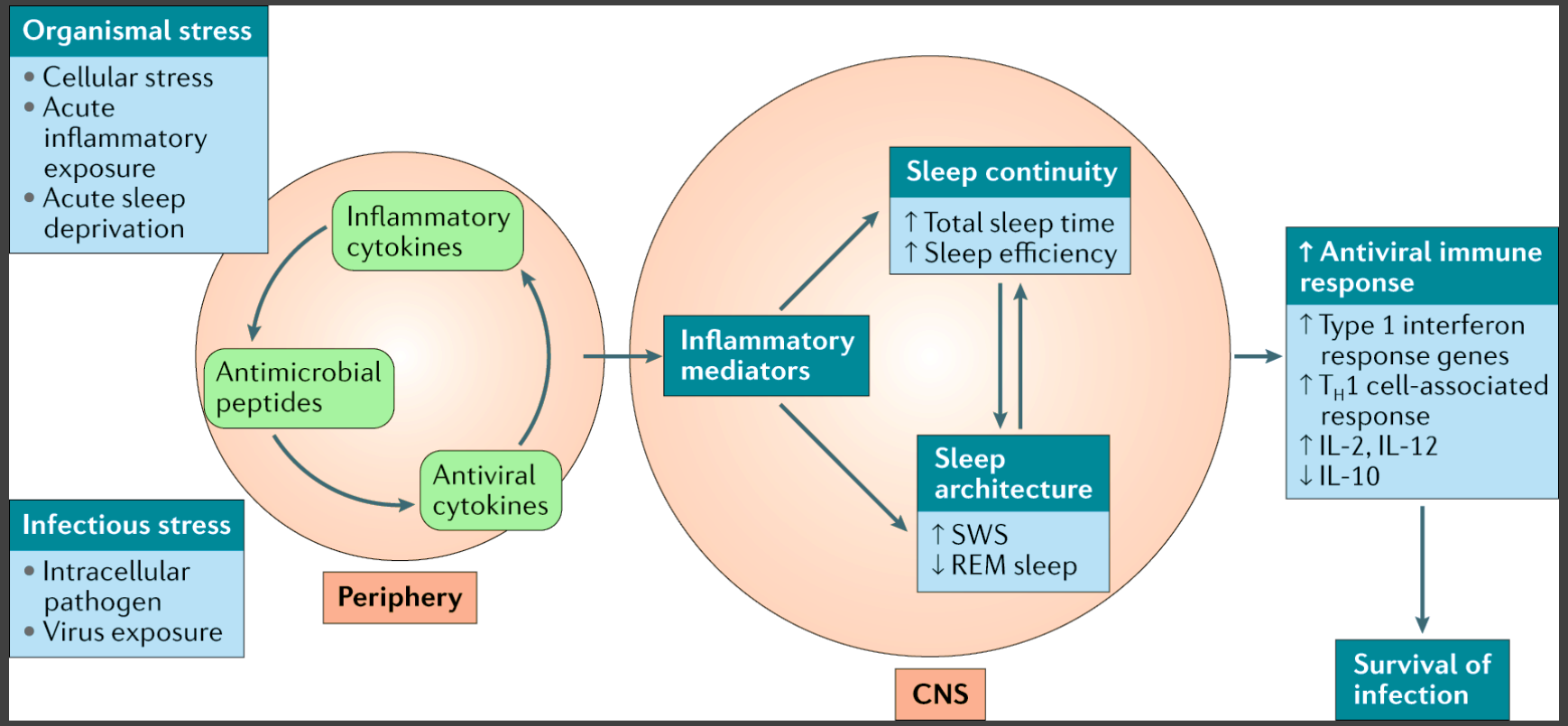
Yoga/Tai Chi

Sleep

Assert yourself- it is okay to say no

Biofeedback

Counseling


Organismal stress
• Cellular stress
• Acute inflammatory exposure
• Acute sleep deprivation
Infectious stress
• Intracellular pathogen
• Virus exposure
Inflammatory cytokines
Antimicrobial peptides
Antiviral cytokines
Periphery
Inflammatory mediators
Sleep continuity
↑ Total sleep time
↑ Sleep efficiency
Sleep architecture
↑ SWS
↓ REM sleep
CNS
↑ Antiviral immune response
↑ Type 1 interferon response genes
↑ T_H1 cell-associated response
↑ IL-2, IL-12
↓ IL-10
Survival of infection

IMPROVING SLEEP

STRICT BEDTIME AND WAKE UP TIME- BE CONSISTENT

ENSURE MATTRESS AND PILLOWS ARE COMFORTABLE

LIMIT CAFFEINE INTAKE, ESPECIALLY 8HRS PRIOR TO BEDTIME

STOP DRINKING FLUIDS WITHIN 2 HRS OF BEDTIME TO MINIMIZE TRIPS TO THE BATHROOM

EXERCISE DAILY (AT LEAST 3 HRS PRIOR TO BEDTIME)

IMPROVING SLEEP

KEEP SLEEP ENVIRONMENT AS DARK AS POSSIBLE LIMITING LIGHTS FROM TV, COMPUTERS AND MOBILE DEVICES

AVOID ALCOHOL NEAR BEDTIME AS THOUGH IT MAY INITIALLY MAKE YOU SLEEPY, IT WILL WAKE YOU UP DURING THE NIGHT ONCE THE EFFECT WEARS OFF

LIMIT DAYTIME NAPS TO 10-20 MIN AND AVOID NAPPING LATE AFTERNOON

KEEP ROOM TEMPERATURE COOL

MINIMIZE HAVING PETS SLEEP NEXT TO YOU IN BED

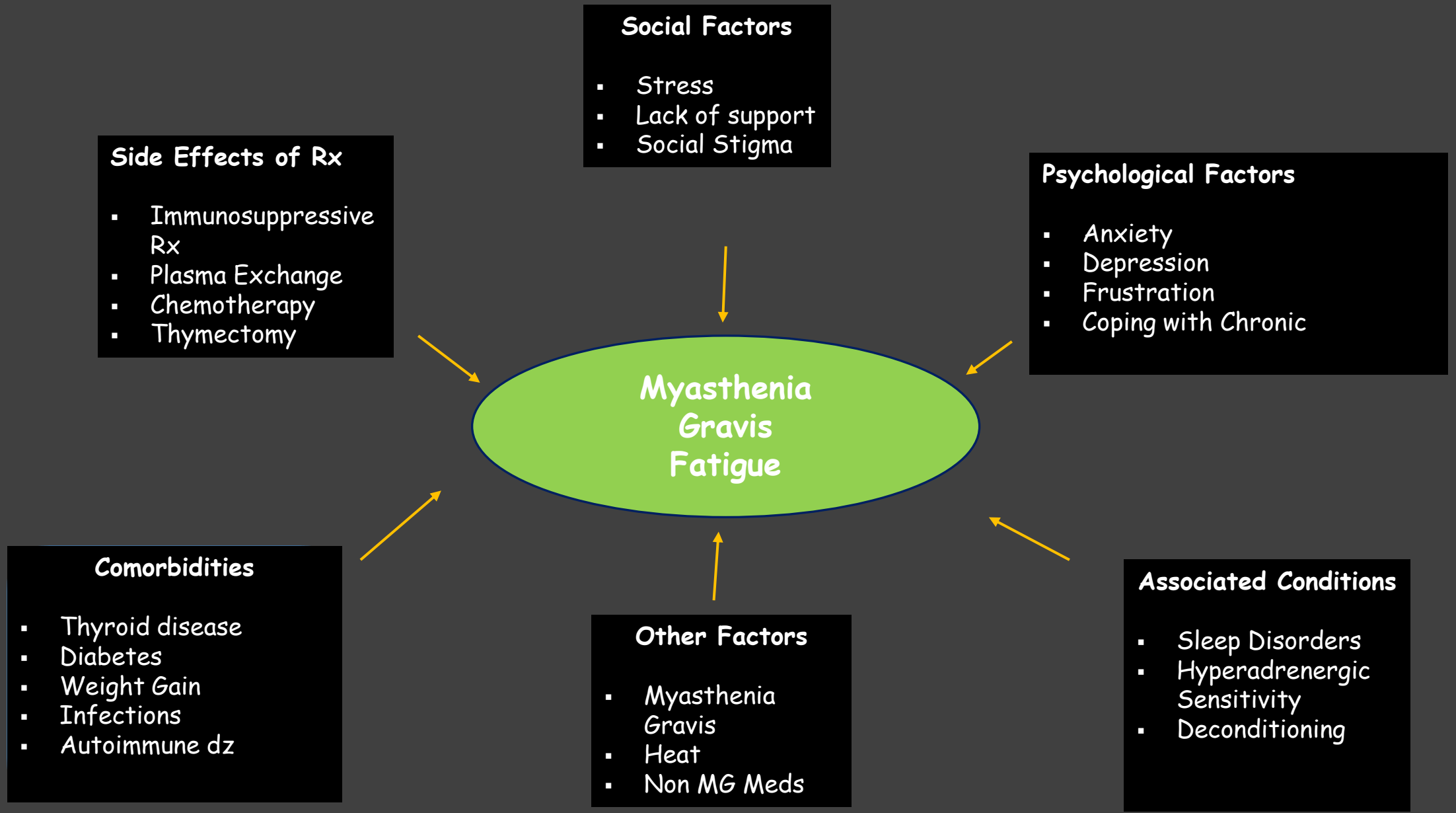
MEDICATIONS THAT AGGRAVATE MG

- **Antibiotics:**
  - Aminoglycosides
  - Fluoroquinolones
  - Tetracyclines
  - Azithromycin
  - Penicillins
  - Sulfonamides
  - Ketek
- **Beta blockers**
- **Calcium channel blockers**
- **Class Ia Antiarrhythmics:** lidocaines

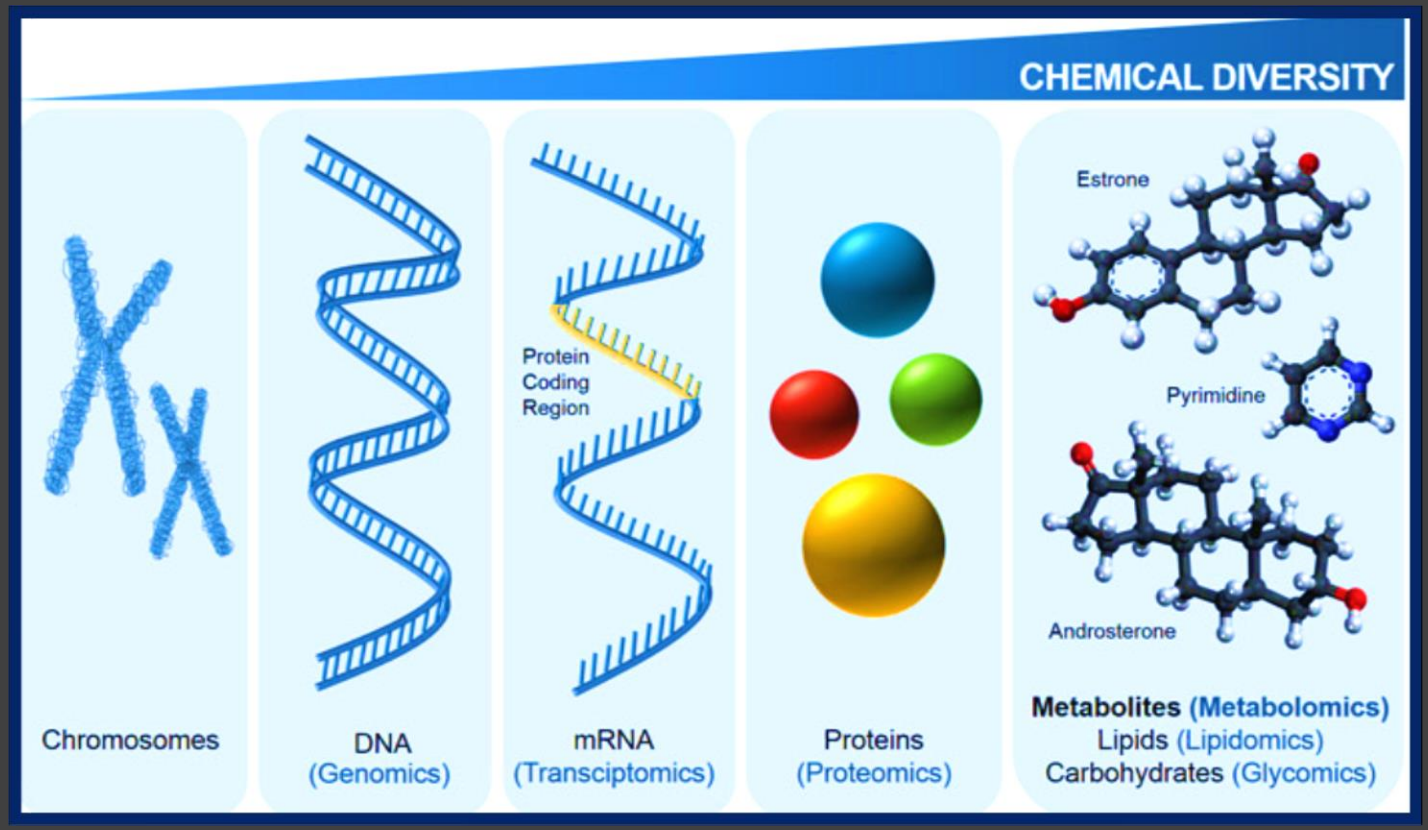
MAGNESIUM
BOTOX

CHECKPOINT INHIBITORS
QUININE

https://myasthenia.org/What-is-MG/Drugs-and-MGg
provides list


Social Factors
Stress
Lack of support
Social Stigma
Side Effects of Rx
Immunosuppressive Rx
Plasma Exchange
Chemotherapy
Thymectomy
Psychological Factors
Anxiety
Depression
Frustration
Coping with Chronic
Myasthenia Gravis Fatigue
Comorbidities
Thyroid disease
Diabetes
Weight Gain
Infections
Autoimmune dz
Other Factors
Myasthenia Gravis
Heat
Non MG Meds
Associated Conditions
Sleep Disorders
Hyperadrenergic Sensitivity
Deconditioning

METABOLOMIC PROFILING OF MYASTHENIA GRAVIS



Beyond the antibodies: serum metabolomic profiling of myasthenia gravis Blackmore, D., Siddiqi, Z., Li, L. et al. *Metabolomics (2019) 15: 109. https://doi.org/10.1007/s11306-019-1571-9*

UPREGULATION OF:

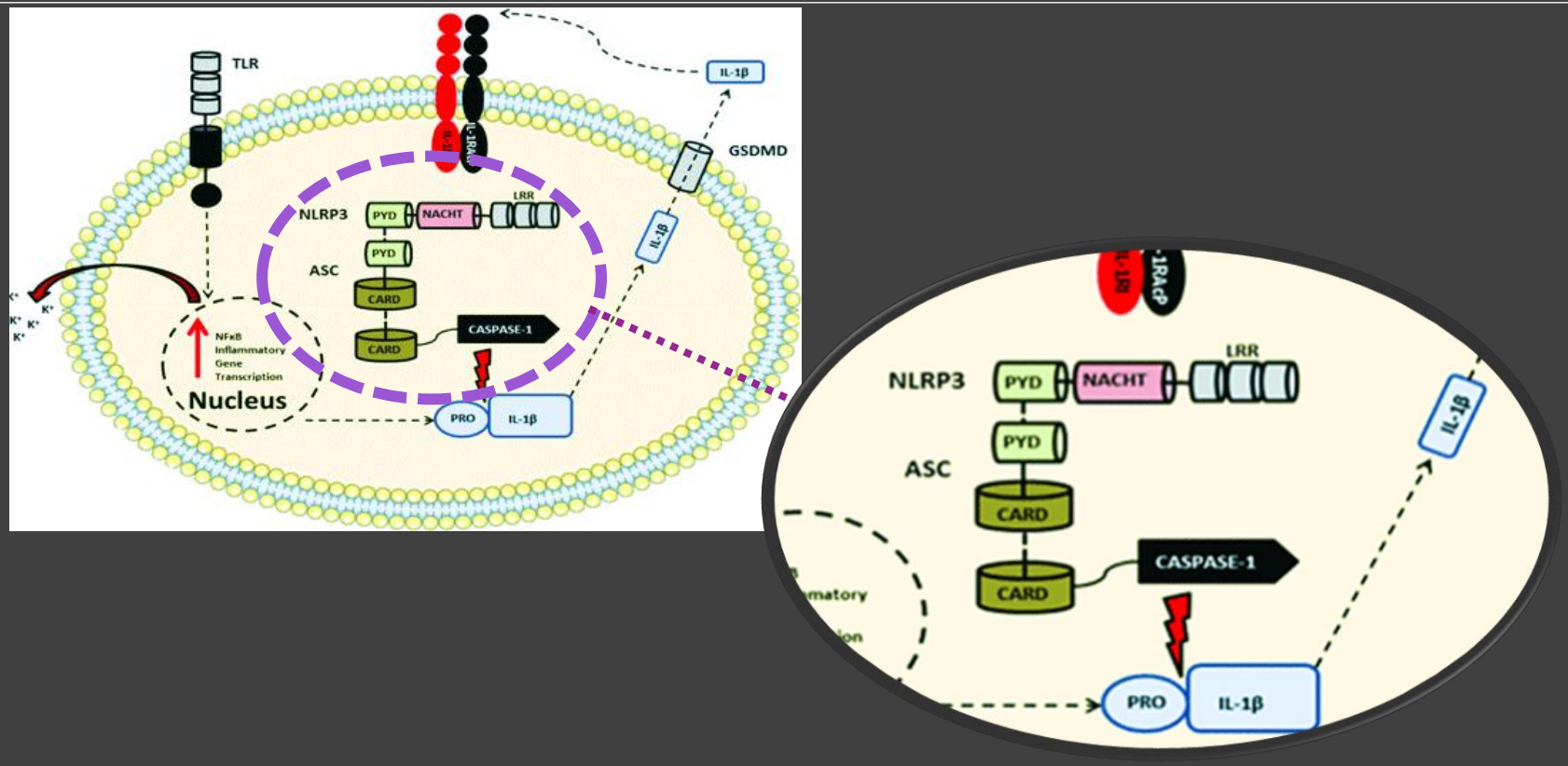
2-Hydroxybutyric acid

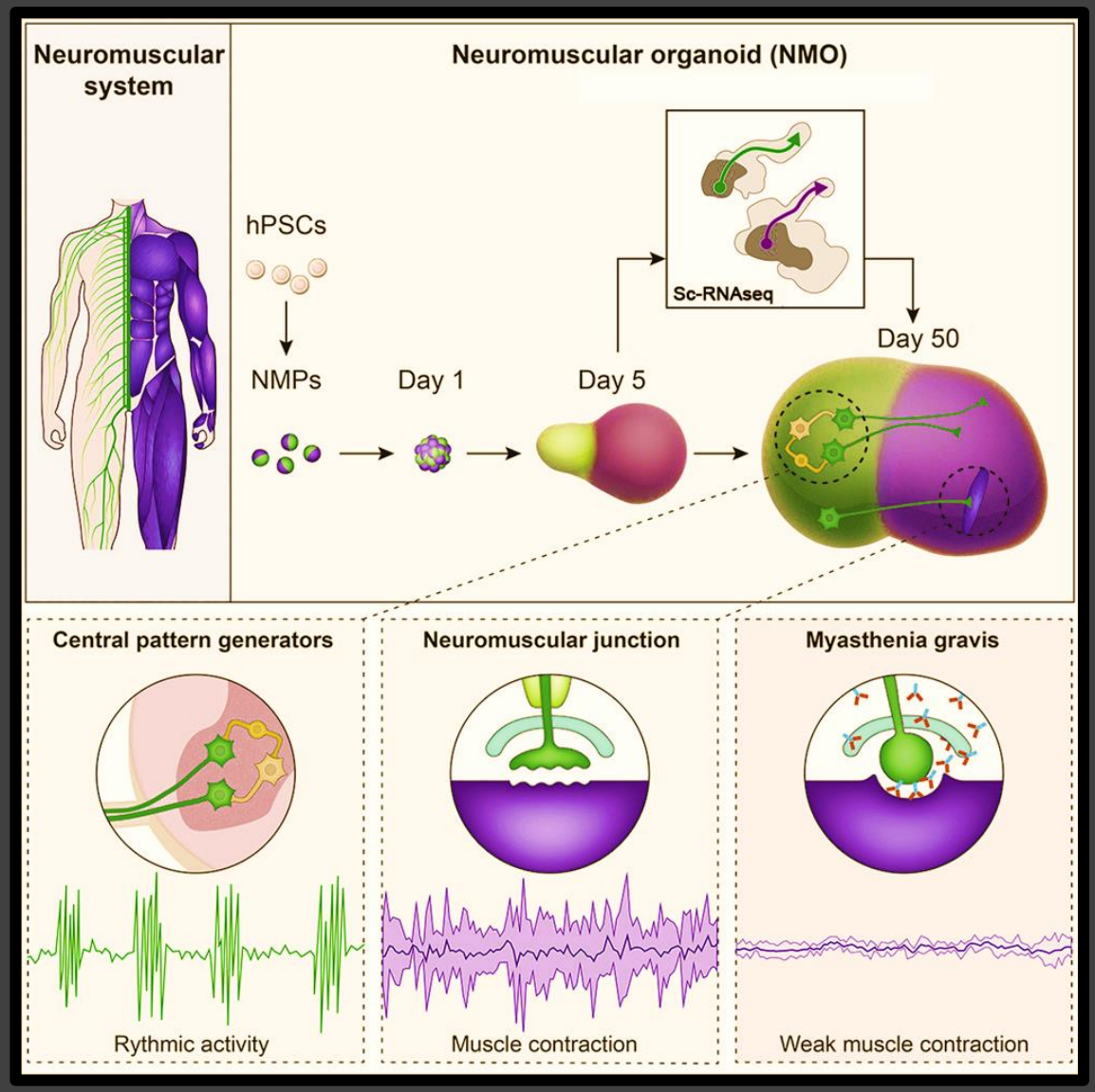
(R)-3-Hydroxybutyric acid : Suppresses activation of the NLRP3 Inflammasome

Acetoacetic acid

2-Ketobutyric acid

Nlrp3 inflammasome




Neuromuscular system
Neuromuscular organoid (NMO)
hPSCs
NMPs
Day 1
Day 5
Sc-RNAseq
Day 50
Central pattern generators
Neuromuscular junction
Myasthenia gravis
Rythmic activity
Muscle contraction
Weak muscle contraction

ZILUCOPLAN

C5 INHIBITOR WITH MINOR ROLE INHIBITING CONVERSION OF C5A TO C6

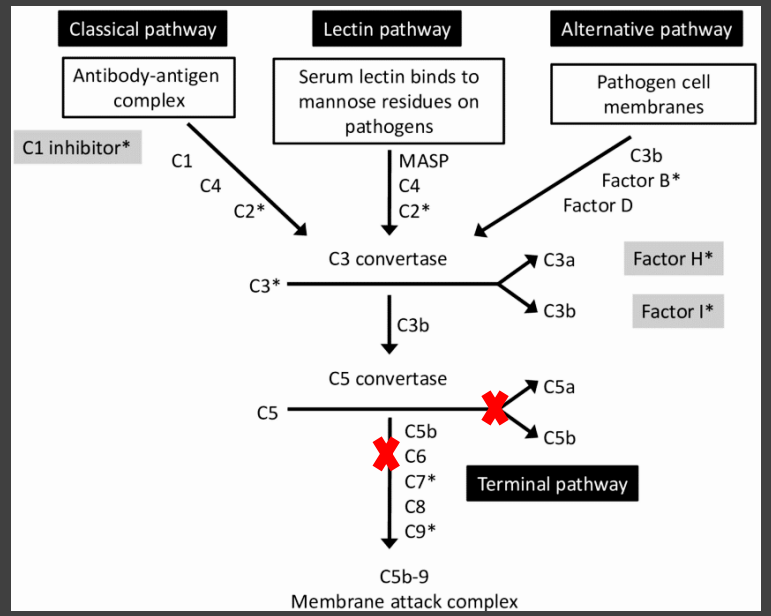
PHASES 2 TRIAL .1MG/KG VS ***.3MG/KG SQ DAILY*** X12 WEEKS

QMG DROPPED BY 6 POINTS

MG-ADL DROPPED BY 3.4 POINTS

SAFE AND WELL TOLERATED

FDA GRANTED ORPHAN DRUG DESIGNATION



PROBIOTICS

ATTENUATES EAMG SYMPTOMS

DECREASES SERUM ANTIRAT AChR AB LEVELS

INCREASES AChR CONTENT

PROBIOTICS INTERACT WITH GALT (GUT ASSOCIATED LYMPHOID TISSUE) AND EPITHELIAL CELLS

Bifidobacterium and lactobacilli

THANK YOU TO MY PATIENTS FOR THEIR SUPPORT