Drug and toxic induced neuromuscular junction disorders

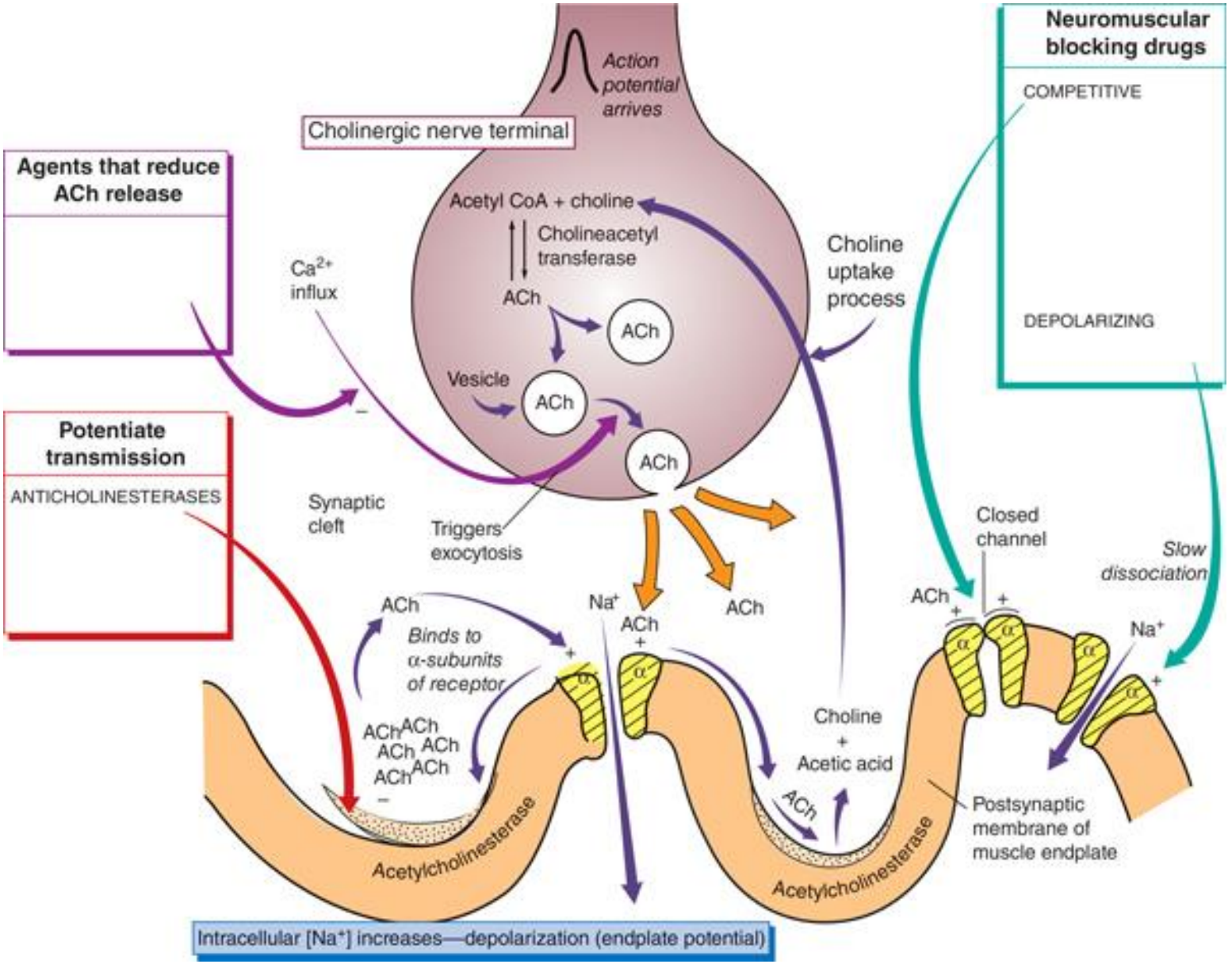
Thanes Termglinchan M.D.

SCAN ME

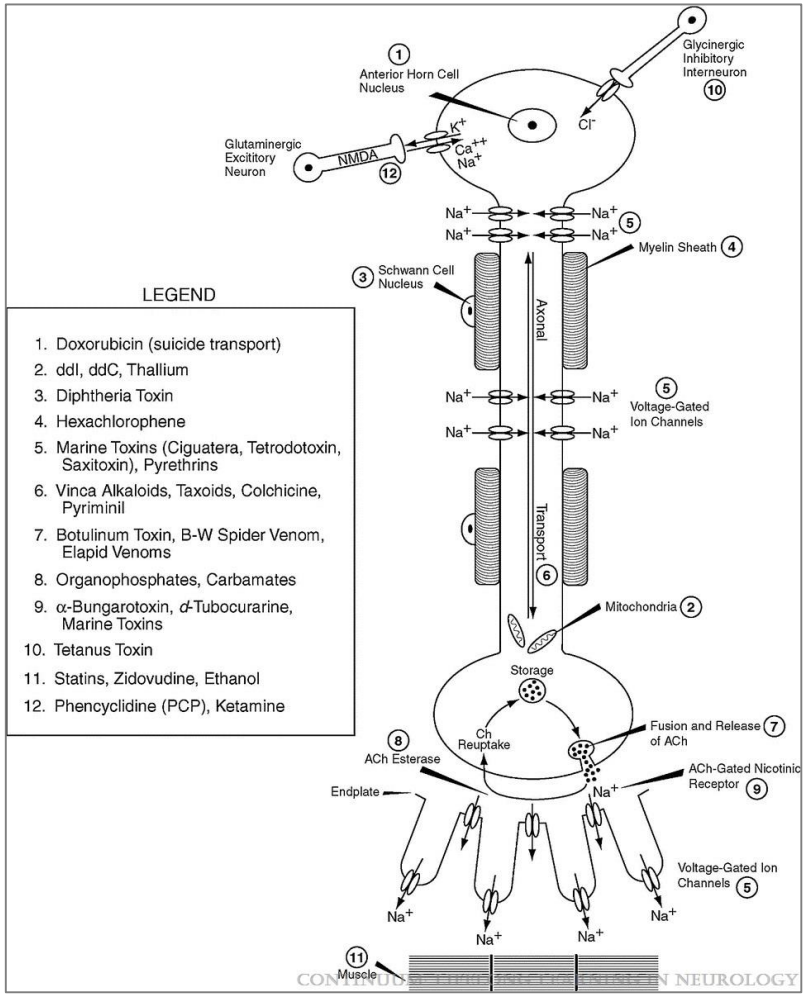
Outline

- Anatomy and physiology of NMJ
- Drug related NMJ disorder
- Toxic related NMJ disorder
- Summary

Anatomy site of drug associated myasthenia



Peripheral neuro toxic agents



Vulnerability of peripheral nervous system motor unit and subcellular structures. A peripheral nervous system diagram depicting sites of action of some biological, environmental, and pharmaceutical agents on motor neuron, axon, and neuromuscular function.

Ach = acetylcholine.

Schaumburg, Herbert; Albers, James W. CONTINUUM: Lifelong Learning in Neurology14(5):11-34, October 2008.

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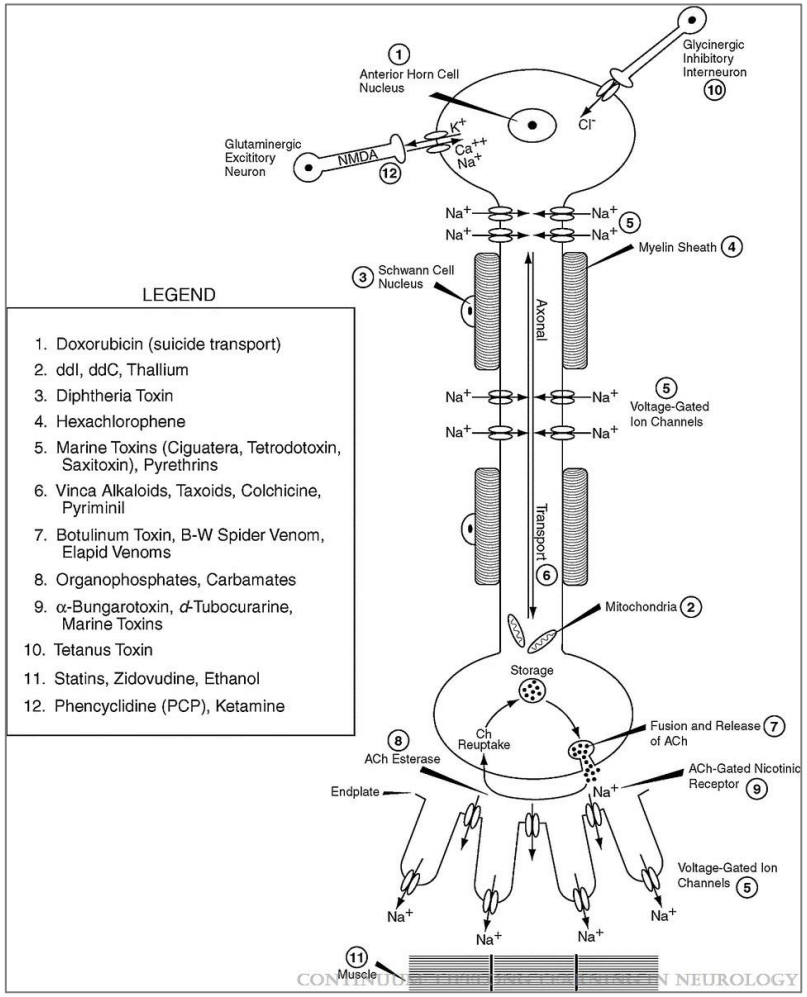

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Drug induced myasthenia

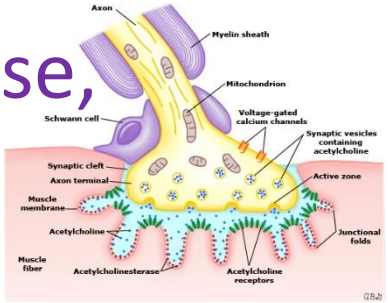
Drug induced myasthenia

1. Worsening MG symptoms or unmask MG e.g. β blocker, aminoglycoside etc.
2. Interfere neuromuscular transmission e.g. anesthetic agent or NMJ blocking agents (+- underlying NM weakness, RF, hepatic failure, electrolyte imbalance) →Delayed recovery of respiratory functions after GA + NMJ blocking agents
3. Induced autoimmune process e.g. D-penicillamine, immune check point inhibitor

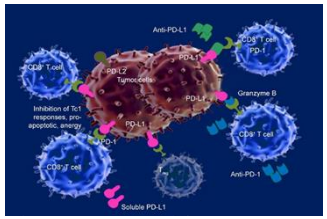
Reduced of safety factor for neuromuscular transmission

Etiology and pathogenesis

- **Acute:** inhibiting synaptic vesicle release, acetylcholine synthesis, acetylcholine receptor activation, or cholinesterase



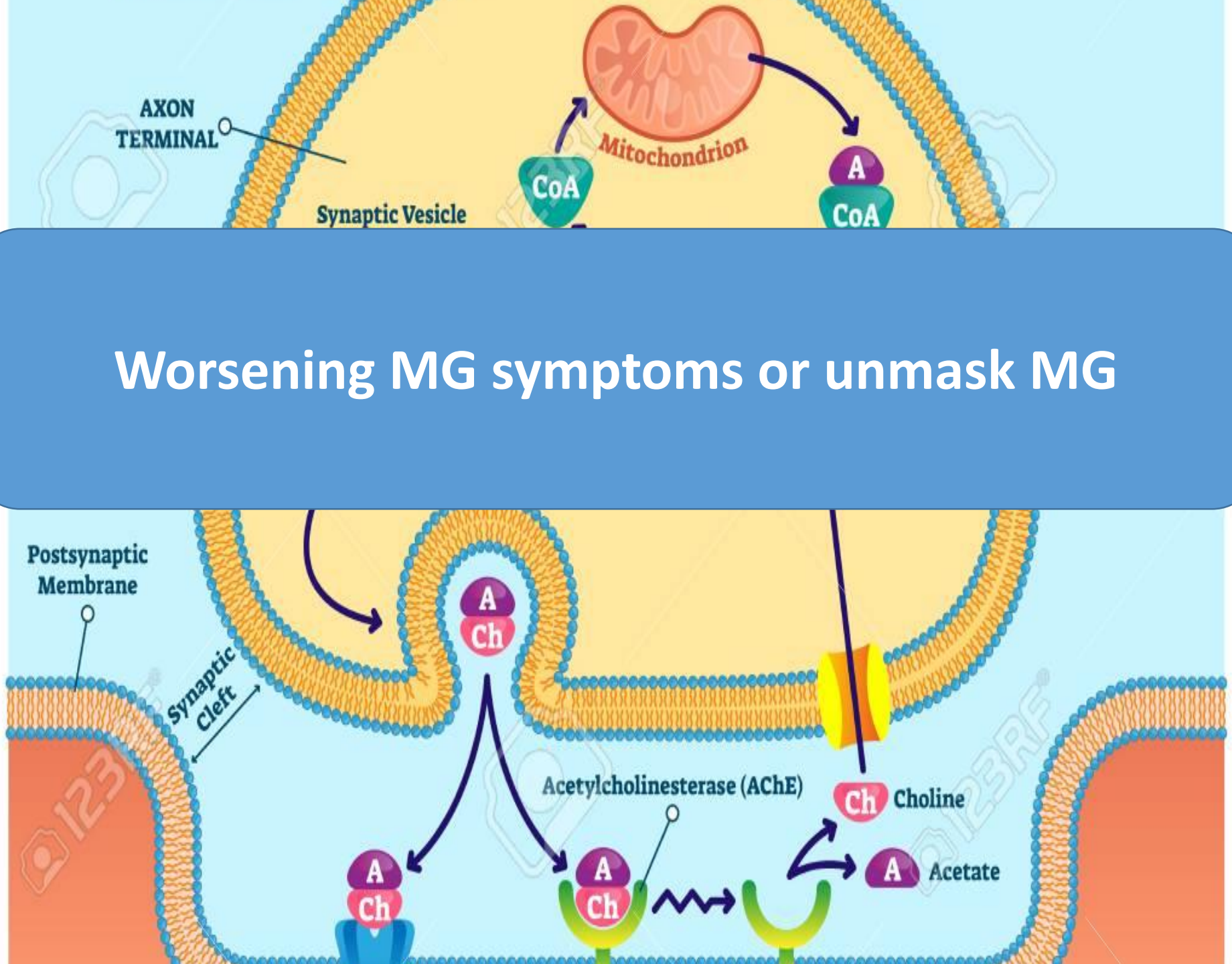
- **Chronic:** A breakdown in self-tolerance, producing a T cell-driven antibody production→form Ab.



Clinical manifestations

- Progressive, and typically symmetric, muscle weakness. ptosis, diplopia, dysphagia, and dysarthria.
- Neuropathy: motor, sensory, autonomic or/and myopathy

Depend on site of action: pre or post synaptic


AXON
TERMINAL
Synaptic Vesicle
CoA
Mitochondrion
A
CoA
Worsening MG symptoms or unmask MG
Postsynaptic
Membrane
Synaptic
Cleft
A
Ch
Acetylcholinesterase (AChE)
Ch
Choline
A
Acetate

Worsening MG symptoms or unmask MG

- Clinical manifestation are similar different subgroups of MG.

Subgroup	Proportion of all MG (%)	Age of onset (years)	Sex (M:F)	Clinical features
Ocular MG	15–25	4–90	3:2	Ptosis, ophthalmoplegia
Early onset AChR-MG	20–25	2–40	1:3	Ptosis, ophthalmoplegia, generalised weakness
Late onset AChR-MG	30–40	.40	3:2	Ptosis, ophthalmoplegia, generalised weakness
MuSK-MG	5–8	2–70	1:3	Predominant ocular, facial and bulbar weakness
Seronegative MG	5–10	10–70	1:2	Ptosis, ophthalmoplegia, generalised weakness

Drug effect on NMJ transmission

Drug class	Drugs	Mechanisms	Risk
Antibiotics	- Aminoglycoside e.g. streptomycin, gentamycin, amikacin - Penicillin, sulfonamides, tetracyclines, fluoroquinolones - Polymyxin B, colistimethate, and colistin - Variconazole	Pre and post synaptic of neuromuscular transmission Block Ach R	+ neuromuscular blocking agents + MG exacerbation/LEMS + alter pharmacokinetic of drugs e.g. + RF or combine neuromuscular blocking agents MG exacerbation
Anticonvulsants	Phenytoin	-Reduce quantal release of Ach - Desensitizing the endplate	
Cardiovascular drugs	-Beta blocker : **propranolol**, practolol, and timolol	Pre and post synaptic of neuromuscular transmission (dose dependent)	MG or LEMS

Drug effect on NMJ transmission

Drug class	Drugs	Mechanisms	Risk
CVS drugs	**Quinine** **Quinidine**	-Presynaptic, ↓release of acetylcholine, -Postsynaptic, with a curare-like action	MG Neuromuscular blocking agents
Corticosteroid		Depolarization of nerve terminals, Reduction in neurotransmitter release, Changes in choline transport, Antagonism of neuromuscular blocking agents, Intracellular potassium depletion	MG and high dose steroid
Neuromuscular blocking drugs Depolarized , Non depolarized	Succinylcholine		Degree of neuromuscular blockade Acid-base status Electrolyte imbalance Underlying MG, LEMS
Ophthalmic drugs	β adrenergic blocking eye drops e.g. timolol maleate Echothioplate	Same as β blocker Long acting Ach Inh = cholinergic weakness	MG/LEMS MG/LEMS + mestinon, succinylcholine

Drug effect on NMJ transmission

Drug class/ indication	Drugs	Mechanisms	Risk
Phenothiazine	Chlorpromazine	a postsynaptic block with a reduction in MEPP and EPP amplitudes.	MG, succinylcholine
Rheumatologic drugs	Chloroquine	Pre and post synaptic Suppresses excitability of muscle membrane Altered immune regulation ? → MG	MG
RA, Wilson, Cystinuria Leukemia, hep C	D-penicillamine (DP) Interferon alpha	Mild, autoimmune ocular MG (AchR ab +) Rx improved after discontinue DP	Genetic predisposing
Others	**D, L-carnitine** **Diuretics** **Magnesium (>5 mEq/L)**	Pre synaptic : ~ hemicholinium Post synaptic block by the accumulation of acylcarnitine esters Hypokalemia	MG + hemodialysis MG exacerbation MG exacerbation, RF and pregnancy with preeclampsia

Drug induced autoimmune process

Immune Checkpoint Inhibitors

D-penicillamine (D-P)

Conditions used:

- Therapy of rheumatoid arthritis, scleroderma, primary biliary cirrhosis, Wilson's disease, and cystinuria.
- Most reports involve patients with rheumatoid arthritis (RA) who have underlying autoimmunity.
- One study showed, Long-term use of D-penicillamine does not produce clinical, electrophysiologic, or significant immunologic evidence of MG in patients with WD.
- D-P-MG is reversible upon drug withdrawal and anti-AChR titers fall gradually.

D-penicillamine (DP)

Onset: 4-9 months after expose DP (occasional 5-8 years)

Clinical: mild, usually ocular MG

Associated HLA Bw35 and DR1

Lab: anti-AChR ab +ve but decreased after withdraw DP

Rx: discontinue DP, symptomatic pyridostigmine, immunosuppressive is not require except severe case.

Prognosis: full recovery within 2-6 months after withdraw DP.

Others medications induced autoimmune MG

- IFN α, IFN β, chloroquine, trimethadone, ritonavir, riluzole
- Lovastatin, pravastatin, simvastatin

Clinical, lab, treatment and prognosis : ~ to expose DP

Anti-MuSK- and anti-AChR-positive myasthenia gravis induced by d-penicillamine

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ABSTRACT

Background: Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction usually caused by antibodies to the nicotinic acetylcholine receptor (AChR) and occasionally to muscle-specific kinase (MuSK). D-penicillamine is a therapeutic agent for several diseases, but can also induce a number of immune-mediated disorders, including MG, as a side-effect. In most patients with D-penicillamine-induced MG, anti-AChR antibodies are detected, but the presence of anti-MuSK antibodies has not been reported previously.
Case: The case reported was a female patient who presented with myasthenic symptoms after D-penicillamine administration for scleroderma.
Results: Both anti-AChR and anti-MuSK antibodies were identified in the patient's serum. The anti-MuSK antibodies were of the IgG4 subclass, as in idiopathic MG. Both types of antibody gradually disappeared after discontinuation of D-penicillamine. A significant improvement in symptoms was observed and the patient gradually became free of MG symptoms, without requiring any treatment for MG. Another four double-positive (anti-AChR and anti-MuSK antibodies) patients were identified during a retrospective study, but none had been treated with D-penicillamine.
Conclusion: D-penicillamine can cause anti-AChR and anti-MuSK antibody-positive MG, a rare phenomenon which is reversed after discontinuation of D-penicillamine treatment.

ICI: Immune check point inhibitor

Table 1. Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.*

Drug	Target	Indication
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency
Pembrolizumab	PD-1	Melanoma, non–small-cell lung cancer, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high microsatellite instability or mismatch-repair deficiency
Atezolizumab	PD-L1	Non–small-cell lung cancer, urothelial carcinoma
Avelumab	PD-L1	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	PD-L1	Urothelial carcinoma

* CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed cell death 1, and PD-L1 programmed cell death ligand 1.

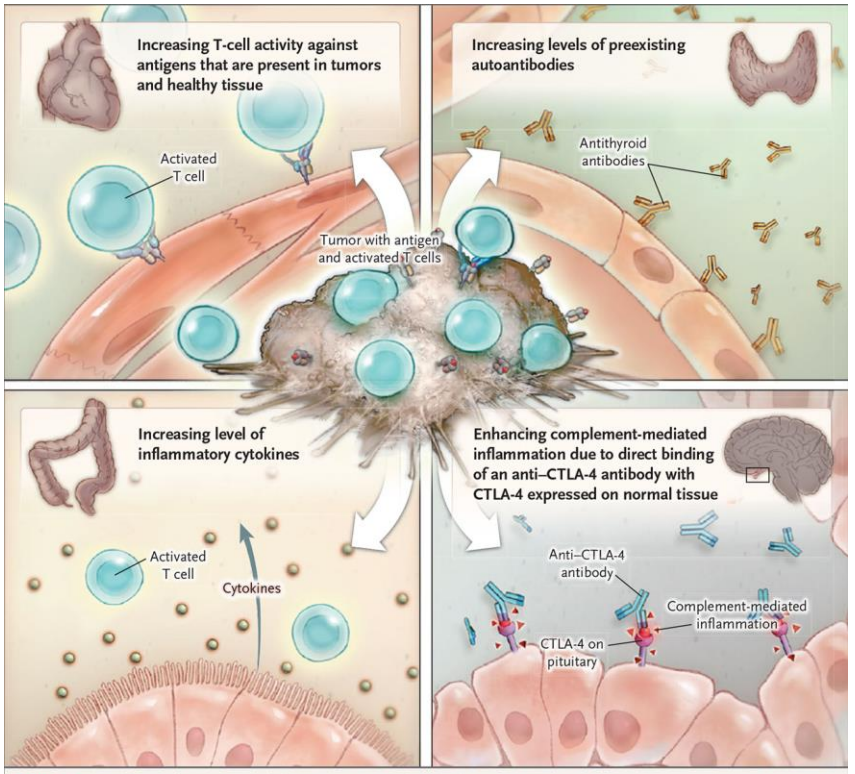
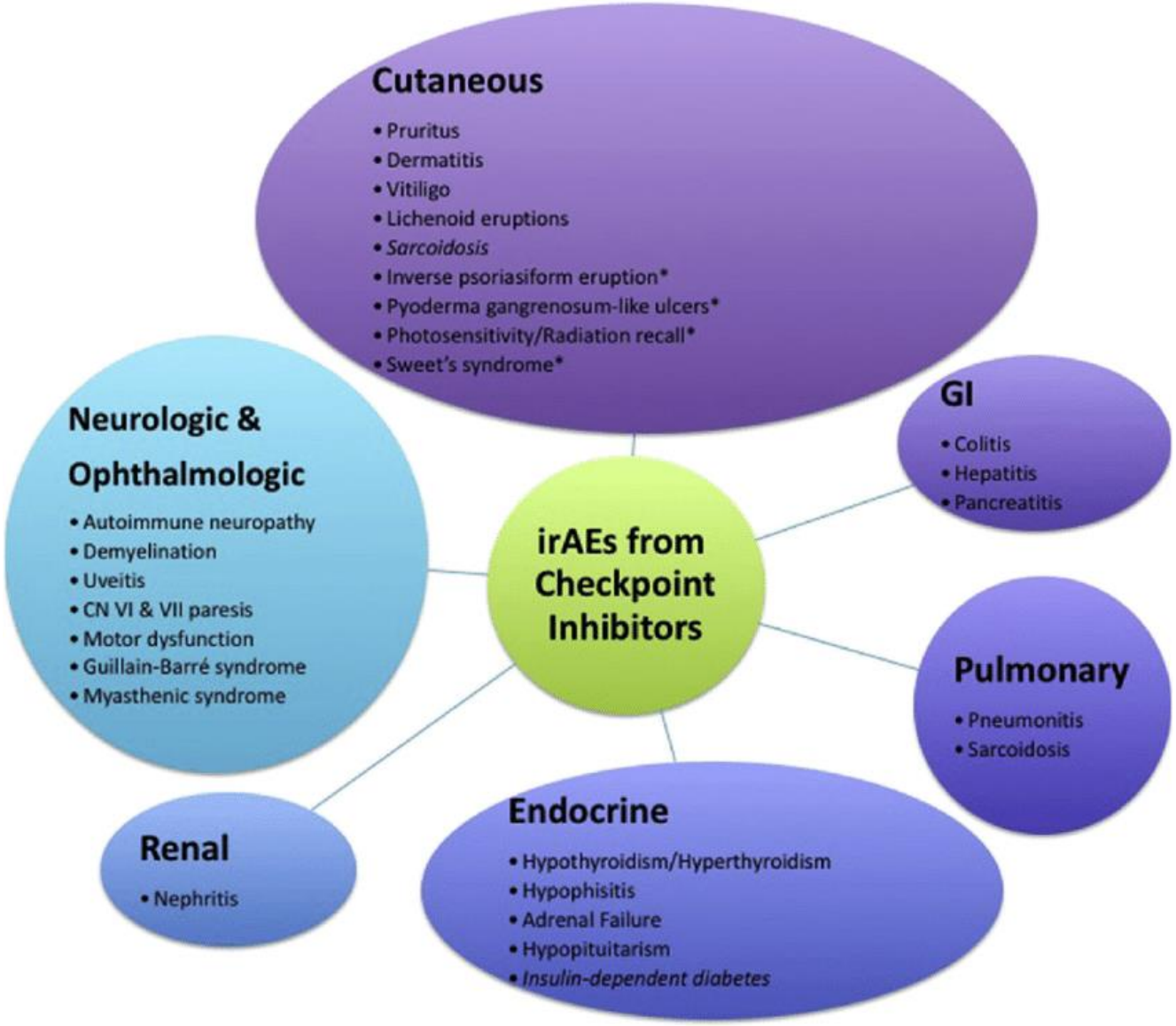


Figure 2. Possible Mechanisms Underlying Immune-Related Adverse Events.
The mechanisms that result in immune-related adverse events are still being elucidated. Some potential mechanisms include increasing T-cell activity against antigens that are present in tumors and healthy tissue, increasing levels of preexisting autoantibodies, an increase in the level of inflammatory cytokines, and enhanced complement-mediated inflammation due to direct binding of an antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4) with CTLA-4 expressed on normal tissue, such as the pituitary gland.

Immune-related adverse events (irAEs)

- Common: primarily with gastrointestinal toxicities, skin disorders, and endocrinopathies.
- Neurological irAEs are rare, representing less than 3% of irAEs.
- Neuromuscular disorders represent the most common neurological irAEs following anti-PD-1, anti-PD-L1, and anti-CTLA-4 treatment, and include myositis, myasthenia gravis, and demyelinating polyradiculoneuropathy.

Adverse events of immune check point inhibitor



Suozzi et al

ICIs-induced neuromuscular

	irMyositis	irMG	irDP	Overlaps
Clinical	Onset within the first 2 months after ICI. **Myalgia:** neck, back, or proximal limbs, preceding weakness. • Often axial weakness with DHS. • Symmetrical proximal weakness. • Frequent ocular Involvement. • Facial weakness and involvement of bulbar muscles (with dysphagia and/or dysarthria) 50% of cases • Respiratory muscle failure possible	Fluctuating and fatigable (30%) muscle weakness, involving ocular, bulbar, and/or respiratory muscles • Typically, generalized MG at onset with rapid progression to myasthenic crisis. • Myositis and myocarditis overlap possible	Acute sensorimotor neuropathy with Hyporeflexia Often cranial nerve involvement	Overlapping syndromes are possible in 16%-25% of cases. The overlapping is possible in different associations between the three pns-irAEs The myocarditis overlap is the most significant as it comes with high mortality rate (50%)

J Peripher Nerv Syst. 2019;24(Suppl. 2):S74–S85.

ICIs-induced neuromuscular

	irMyositis	irMG	irDP	Overlaps
Laboratory work-up	Specific myositis antibodies are usually negatives.	Anti-AChR antibodies positive (57%-83%). No correlations anti-AChR titers and irMG severity HyperCKemia possible pointing to an overlap syndrome	Anti-ganglioside antibodies when tested, usually negatives. CSF with albumin cytological dissociation. Notably mild lymphocytosis can be associated (10-15)	CK and troponin testing advised for each suspicion of pns-irAEs
ENMG	Myopathic motor unit potentials in 72% to 100% of patients with positive sharp waves and/or fibrillation Potentials.	Decrement on low-frequency RNS at a frequency of 3 Hz and increased jitter on single fiber EMG 50%. Frequent concurrent myositis	Evidence of demyelination: sural sparing pattern, prolonged F-wave latencies, and decrease Motor Conduction velocities and sometimes conduction block	Always proceed to electrophysiological exploration

ICIs-induced neuromuscular

	irMyositis	irMG	irDP	Overlaps
Others	Biopsy is recommended • Dominance of CD68+ and CD8+ cells and CD4+ cells on other cases • Multifocal necrotic myofibers with sparse T-cell infiltrates No significant number of CD20+ cells	Variable response to Cholinesterase Inhibitors prostigmine, or icepack test can be positive	Biopsy if necessary • Invasion of inflammatory cells • Large epineurial Perivascular inflammatory collections composed of primarily T lymphocytes	Respiratory and cardiac evaluation (ECG and echocardiogram) to be recommended systematically

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Immune-related myasthenia gravis (irMG)

- Exacerbation of a pre-existing MG or to a newly MG.
- Isolated irMG seems to be a rare condition: irMG and irMyositis → risk for MG crisis.
- Most patients were men, with median age around 70 years, receiving anti-PD-1 therapy.
- Onset: 2 to 6 weeks from the start of ICIs treatment.
- Clinical: fluctuating muscle weakness involving ocular, bulbar, and/or respiratory muscles.
- A rapid progression to a myasthenic crisis is observed in up to half of the patients.

Suzuki S, Ishikawa N, Konoeda F, et al., Neurology. 2017; 89(11):1127-1134.

Immune-related myasthenia gravis (irMG)

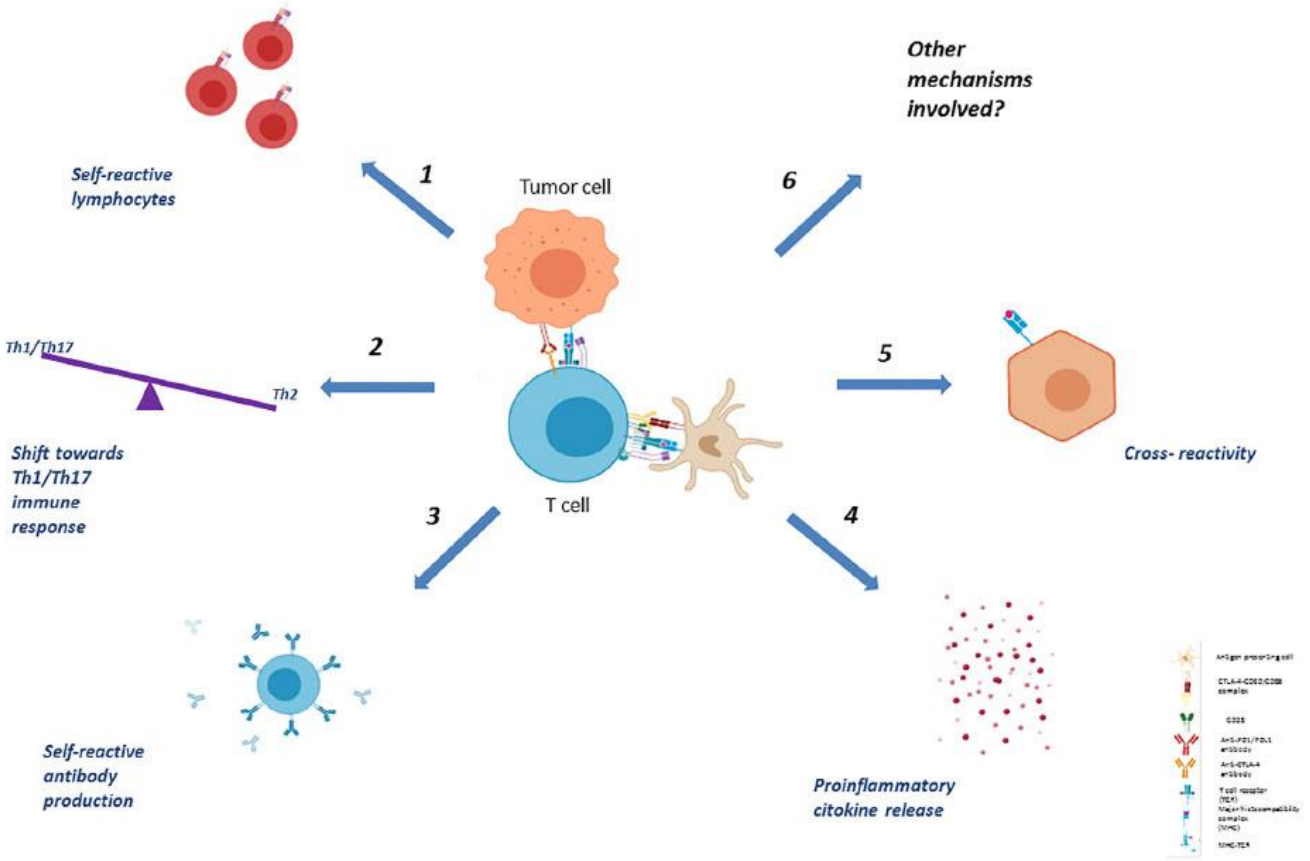
- Abnormal RNS and SFEMG were identified only in half of the patients tested.
- Anti-AChR ab +ve 57% to 83% of patients.
- A single case report of a patient with relapsing ocular MG and positive anti-AChR and anti-muscle-specific kinase (MuSK) antibodies following nivolumab treatment.
- The great majority of patients with irMG requires prompt hospitalization and one or multiple lines of immune-modulatory treatments

Suzuki S, Ishikawa N, Konoeda F, et al., Neurology. 2017; 89(11):1127-1134.

PHYSIOPATHOLOGICAL MECHANISMS

- Removal of self-tolerance appears to be the trigger of immunotherapy toxicities.
- Potential mechanisms may relate to antigens shared between affected tissue and tumor leading to a cross reactivity between tumor neo-antigens and normal tissue antigens favoring the development of irAEs by immunotherapy.

Pathogenesis of immune-related neuromuscular toxicity



J Peripher Nerv Syst. 2019;24(Suppl. 2):S74–S85.

Diagnostic work up

- Alternative causes (metabolic, endocrine, infectious, and toxic) or Tumor progression and perineural invasion.
- CK, trop T , Testing for onconeural and organ-specific autoantibodies
- anti-AChR, anti-MuSK, anti-Ca++ channel and striatational antibodies
- ANA, dsDNA, anti-SNA, and ANCA and anti-ganglioside antibodies
- NVC/EMG/RNS
- LP: cytology or infection
- CNS imaging
- Nerve or muscle biopsy

Treatment

- Standardize the treatment of pns-irAEs based on the grading of toxicity, according to common terminology criteria for adverse events (CTCAEs) criteria.
- grade 1-2 CTCAE toxicities: temporarily withhold ICIs.
- grade 3-4 toxicities: permanent ICIs discontinuation.
- High-dose corticosteroid therapy,
- Steroid-resistant cases (fails to respond within 1 week): IvIg, PLEX → 3rd tocilizumab, infliximab, rituximab, mycophenolate, methotrexate, and cyclophosphamide.

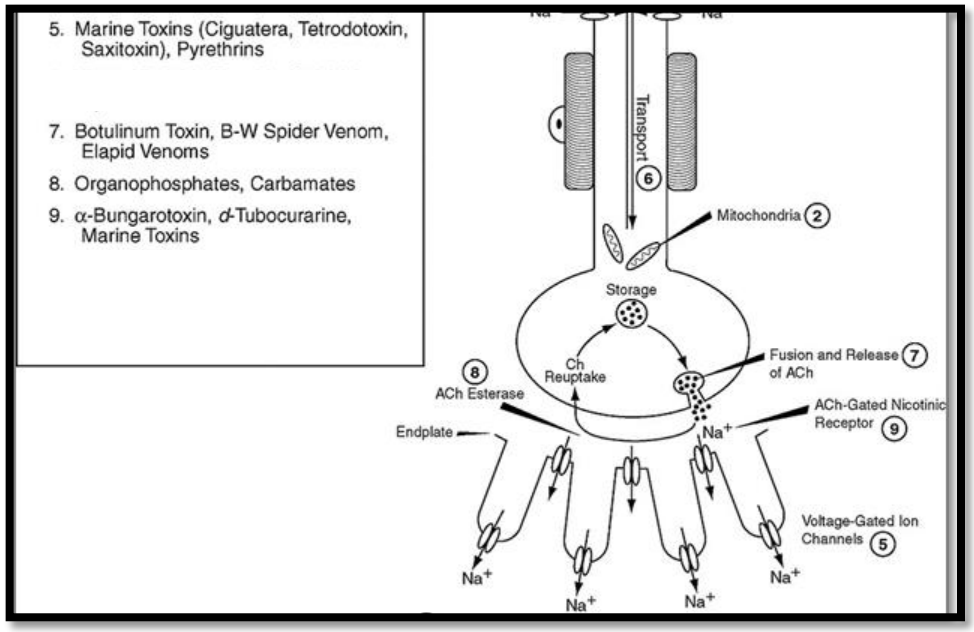
Prognosis and complications

- Complete recovery after stop medications (-18 months).
- Depend on underlying disease e.g. unmask MG
- Except autoimmune MG induced by immune check point inhibitor

Toxic induced NMJ disorder

Toxic-induced myasthenic syndromes

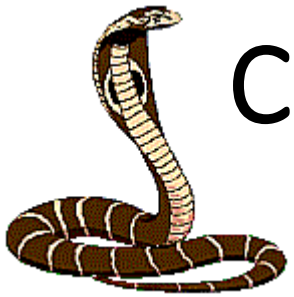
Mechanism: presynaptic, post synaptic, sodium channel blockage and Acetyl choline esterase inh.



- **α or β bungarotoxin**
- **Botulism**
- **Organophosphate poisoning**
- **Tetrodotoxin and sasitoxin**

Thai snake venoms

- 160 species of snakes belonging to ***9*** families.
- 46 species of 2 families are venomous.
- 24 are land snakes.
- They are divided in to 2 families : ***Elapidae*** **and** ***Viperidae.***
- Elapid venoms contain potent neurotoxin: postsynaptic and presynaptic neurotoxins, on the basis of their sites of action at the neuromuscular junction. They cause muscular paralysis.
- Among the neurotoxic snakes (cobra, king cobra, krait) found in Thailand, cobra is most important since it is well known and widely distributed in all parts of the country especially in central Thailand.



Common snake in Thailand

Elapidae

- Cobra, king cobra, krait: neurotoxin
- **Sea snake:** rhabdomyolysis.

Viperldae

Vasculotoxicity and hematotoxicity

- **Russell's viper** *(Vipera russelfii siamensis),*
- **Green pit viper** *(Trimeresurus species)*
- **Malayan pit viper** *(*Agkistrodon rhodostoma or Callaselasma rhodostoma).

Thai cobra *(Naja Kaouthia)* venom

- Venom has a postsynaptic neurotoxin.
- It binds to the nicotinic acetylcholine receptor at the motor end plate, and is a highly potent neuromuscular blocking agent. Receptor binding is reversible.
- The venom is rapidly absorbed from the site of bite, and the blood venom level rapidly decreases within 20-30 hours with the half life of 7 1/2 hours.
- Thus, the victim can spontaneously recover without antivenom treatment if respiration is maintained by a respirator. Skin necrosis occurs in **46%** of the patients.

อาการและอาการแสดงเฉพาะงูในกลุ่ม Elapidae

- **อาการเฉพาะที่**: จะมีอาการปวด บวม แดงร้อน ตรงตำแหน่งที่ถูกกัดจาก increased vascular permeability ซึ่งเป็นฤทธิ์ของเอ็นไซม์หลายชนิดคือ proteases phospholipases hyaluronidase และสารคัดหลั่งต่างๆ เช่น histamine kinins 5-hydroxytryptamine เป็นต้น เว้น งู สามเหลี่ยม และงูทับสมิงคลากัด

- **อาการและอาการแสดงเฉพาะ:** อาการทางประสาท (neurotoxicity) เริ่มจากผู้ป่วยจะมีอาการหนักที่หนังตาบน ตาพร่า มองเห็นเป็นสองภาพ (double vision) ชาที่ริมฝีปาก และมีน้ำลายมาก ต่อมาจะพบหนังตาตก ลืมตาไม่ขึ้น ตากลอกไปมาไม่ได้ ซึ่งจะเกิดภายใน 1-2 ชั่วโมงภายหลังถูกงูกัด และในที่สุดจะไม่สามารถหายใจ

อาการและอาการแสดงเฉพาะงูในกลุ่ม Elapidae

- อาการต่างๆ เหล่านี้จะกลับคืนสู่ปกติ ภายในเวลาเป็นชั่วโมงภายหลังได้รับเซรุ่มแก้พิษงู หรือยา anticholinesterase แต่ถ้าผู้ป่วยได้รับการรักษาแบบประคับประคอง supportive treatment กว่าอาการจะกลับคืนสู่ปกติ อาจใช้เวลานาน 2-7 วัน

- **การตรวจทางห้องปฏิบัติการ:** CBC, coagulation, LFT, CK, ECG

อาการและอาการแสดงเฉพาะงูในกลุ่ม Elapidae

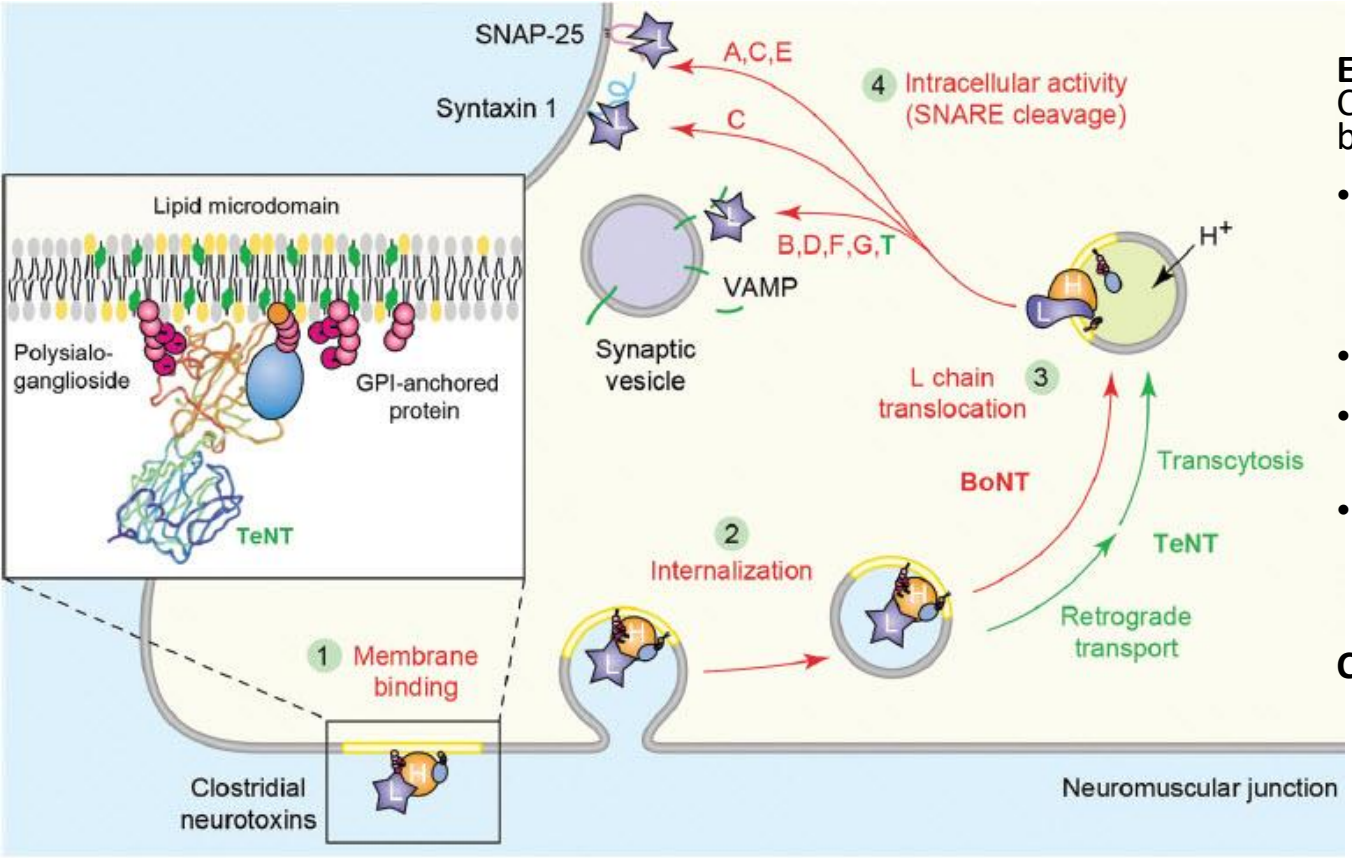
Immunodiagnostic:

1. **Venom antigen detection:** น้ำยาทดสอบสำเร็จรูป (kit test) รู้ผลว่าถูกงูชนิดไหนกัดในเวลา 15-30 นาที วิธีการทดสอบคล้ายการตรวจปัสสาวะดูการตั้งครรภ์ ตัวอย่างที่นำมาตรวจหาพิษงูใช้เลือด น้ำเหลือง ปัสสาวะ หรือ tissue fluid ที่ได้จากการดูดแผล (wound aspiration)
2. **Venom antibody detection :** ผู้ที่ได้รับพิษงูสู่ร่างกายจะสร้างภูมิต้าน (antibody) ต่อพิษงูขึ้น และภูมิต้านนี้จะอยู่ได้นานเป็นเวลาหลายปี

หลักการรักษาผู้ถูกงูกัด

1. ผู้ป่วยถูกงูพิษกัดใช่หรือไม่ จำเป็นต้องให้เซรุ่มแก้พิษงูหรือไม่ ถ้าไม่ทราบชนิดงู แนะนำให้นอนรพ.สังเกตอาการ
2. ขนาดและวิธีการให้เซรุ่มแก้พิษงูและข้อควรระวัง : มีผู้ป่วยเพียงหนึ่งในสามเท่านั้นที่ได้รับพิษงูเข้าสู่กระแสโลหิต และเกิดอาการของพิษงูชนิดนั้นๆ ซึ่งจำเป็นต้องได้รับการรักษาโดยเซรุ่มแก้พิษงู ต้องใช้เซรุ่มแก้พิษงู (antivenom) ให้ตรงกับชนิดของงูที่กัดโดยให้ปริมาณที่มากพอ ถ้าเป็นพิษต่อระบบประสาท anticholinesterase อาจช่วยชีวิตผู้ป่วยได้ atropine sulfate 0.6 mg iv, neostigmine methylsulphate 50 - 100 ug/kg + atropine q 4 hours.
3. การรักษาแผลและภาวะแทรกซ้อน

Botulism



Etiology: Botulinum toxins from Clostridium botulinum (human botulism :A, B, E, F)

- **Mechanism:** interference with proteins involved in neurotransmitter vesicle fusion:
- **Types A and E affect** SNAP-25,
- **Types B, D, F, and G** affect synaptobrevin,
- **Type C affects** syntaxin and SNAP-25

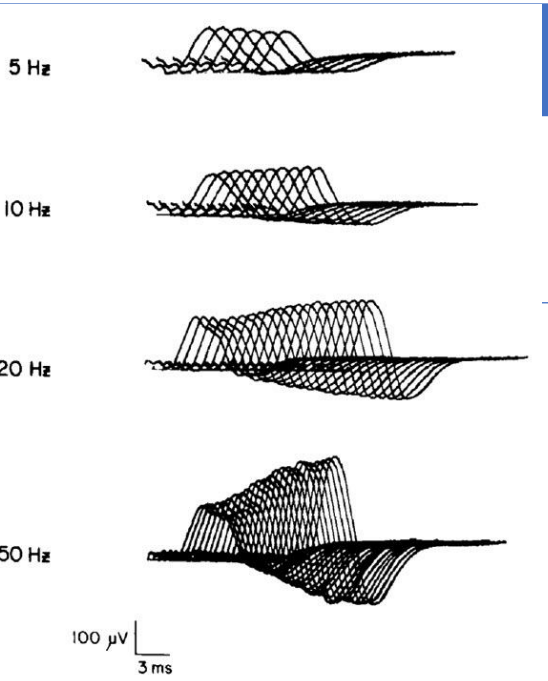
Clinical: ANS and motor nerve

Botulism

Bacterium	Clostridium botulinum
Toxin	Botulinum toxin (types A–G)
Location of toxin action	Presynaptic terminals of neuromuscular junction
Mode of acquisition	• Home-canned food, inadequately refrigerated or cooked food (foodborne) • Injection drug use (Wound botulism), • Honey (Infant botulism), • Iatrogenic : high dose botulinum toxin A or B • Adult intestinal colonization (unknown source)
Major clinical features	**Classic pentad:** • dry mouth, • nausea/vomiting, or abdominal pain → foodborne. • dysphagia, diplopia, • fixed dilated pupils; • followed rapidly by extremity Weakness

Botulism

Diagnosis	• Serum or stool culture, • Toxin identification by mouse-based assay or EL • EMG/RNS
NCS and EMG findings	• Decreased compound muscle action potential (• Decremental response to low frequency repetit • Incremental response (facilitation) to high-frequ • Persistence of post-tetanic facilitation, • Short-duration low-amplitude motor unit poter • Increased jitter on single fiber EMG, • Normal velocities/latencies
Treatment	• Antitoxin (infant: human-derived botulism immunoglobulin [BIG-IV]; • Adult: heptavalent botulinum antitoxin, • Antibiotics for wound botulism only, • Supportive care
Prevention	• Proper food preparation and canning techniques, • avoidance of honey for infants



Tetrodotoxin and sasitoxin

ปลาปักเป้า (puffer fish) และไข่แมงดาทะเล (horseshoe crab)

สัตว์ที่มีสารพิษชนิดนี้ผสมอยู่ได้แก่

- ปลาปักเป้าทั้งน้ำจืดและน้ำเค็ม
- หอยบางชนิด (Japanese ivory shell, trumpet-shell)
- แมงดาทะเล (horseshoe crab) เฉพาะแมงดาถ้วย
- ปลาหมึกบางชนิด (blue-ringed octopus)

สารพิษเตโตรโดทอกซินและเซซิทอกซิน ในปลาปักเป้า หรือถูกเก็บไว้ในตับ รังไข่ ลำไส้และ ผิวหนัง ส่วนแมงดาทะเลจะมีมากในไข่แมงดา

สารพิษทั้ง 2 ชนิดเป็นสารประกอบซึ่งทนต่อความร้อนได้ดี

Tetrodotoxin and sasitoxin

Pathophysiology

- Sodium channel blockade: muscle, motor and sensory nerve

Clinical manifestation:

Onset: 10-45 minutes after expose toxin

Clinical:

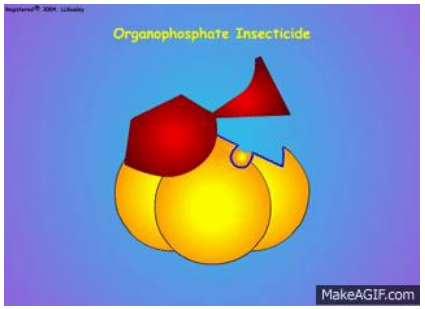
- Perioral and tongue numbness, hand and feet numbness
- Ascending paralysis, ptosis, dysphagia and respiratory failure.
- Hypotension and dysarrthymia

Duration of symptoms: 1-3 days

Diagnosis : clinical and exposure

Rx: NPO, respiratory care, decontamination (lavage + activated charcoal)

Organophosphate poisoning and carbamates



- เป็นสารเคมีกำจัดแมลงที่มีใช้กันอย่างแพร่หลายมาก

พิษจลนศาสตร์

- Organophosphates เป็นสารพิษในกลุ่มที่ถูกดูดซึมได้ดีทางผิวหนัง ทางเดินอาหารหรือแม้แต่ทางปอด
- Metabolite ส่วนใหญ่จะถูกขจัดทางไต half-life ของ parent compound เช่น malathion จะประมาณ 3 ชั่วโมง parathion ประมาณ 2.1 วัน แต่ metabolite ของ parathion อาจอยู่ในร่างกายนานถึง 27 วัน

Organophosphate poisoning and carbamates

Organophosphates

Azinophos-methyl (Gluthion)
Carbophenothion (Tri-thion)
Chlorthion
Diazinon (Basudin)
Dicrotophos (Bidrin)
Dicapthion (Di-Captan)
Ethion (Nialate)
Fenthion (Baytex)
Malathion (Cythion)
Parathion
Phosphamidon (Dimecron)
TEPP (Bladan, Tetron)
Tichlorfon (Dipterex, Tugon)

Carbamates

Aldicarb (Temik)
Aminocarb (Metacil)
Bendiocarb (Ficam)
Propoxur (Baygon)
Carbaryl (Sevin)
Carbofuran (Furaxdan)
Methomyl (Lannate, Nudrin)
Mexacarbate (Zectron)

Organophosphate poisoning and carbamates

Stage	อาการ และอาการแสดง	การรักษา
1 Acute (2-3 วัน) 1 Sympathetic (ภายใน 6 ชั่วโมง) 2 Parasympathetic 3 Neuromuscular junction 4 Solvent effects	 Tachycardia, HT bronchial secretion, N/V, bradycardia, hypotension muscle twitching, opsoclonus, chill , paralysis cardiac arrhythmias, coma	 2-PAM atropine และ 2-PAM - -
2 Subacute (1-2 สัปดาห์) 1 Recurrent 2 CNS 3 Intermediate syndrome 4 Torsades de Pointes	 Confusion, coma, seizure Weakness without twitching, CN deficit, RF prolonged QT interval และ ventricular arrhythmias	- - อาการนี้อาจเป็นอยู่ 8-14 วัน แล้วจะดีขึ้นเอง
3 Chronic (เดือน) 1 Delayed polyneuropathy 2 Neuropsychiatric	 distal weakness ของแขน ขา cuff pain, paresthesia ของปลายมือ ปลายเท้า	-

การตรวจทางห้องปฏิบัติการ

โดยทั่วไปแล้วมักจะใช้ระดับ cholinesterase enzyme

โดยทั่ว ๆ ไปผู้ป่วยจะไม่มีอาการถ้าระดับ cholinesterase สูงกว่า 50% ของค่าปกติ

ในรายที่มีภาวะเป็นพิษน้อยระดับอยู่ประมาณ 20-50%

พิษปานกลางประมาณ 10-20%

ในผู้ป่วยที่มีอาการรุนแรงค่า cholinesterase จะลดลงเหลือน้อยกว่า 10%

การรักษา

- การรักษาโดยการประคับประคอง
- Decontamination โดยการลดการดูดซึม และเพิ่มการกำจัดสารพิษออกจากร่างกาย

ยาต้านพิษ

- **Atropine** เป็น noncompetitive antagonist ของ muscarinic receptor จึงสามารถแก้อาการของ parasympathetic overactivity ได้ทั้งหมด
- **Oximes** ที่ใช้กันบ่อยๆ อยู่ในรูป 2-PAM เป็น specific antidote ของ organophosphates **Oximes** ที่ใช้กันบ่อยๆ อยู่ในรูป 2-PAM เป็น specific antidote ของ organophosphates แต่ไม่ผ่าน BBB

Summary