The Neuromuscular Junction: Neurophysiology and Common Disorders

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Disclosures

- I have consulted for Alexion Pharmaceuticals
Learning Objectives

- Describe the events occurring at the NMJ that leads to successful neuromuscular transmission
- Describe the presentation, pathophysiology, diagnostic testing and treatment options for myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS), and botulism
- Contrast the symptoms and signs of MG, LEMS, & botulism
The Neuromuscular Junction

1. Action potential
2. Voltage-gated calcium channel
3. Vesicle of acetylcholine
4. Voltage-gated Na+ channel
5. Plasma membrane of muscle fiber
6. Acetylcholinesterase
7. Acetylcholine receptor site
8. Motor end plate
9. Terminal button
10. Muscle fibers
11. Axon terminals
12. Action potential propagation in muscle fiber
13. Neurotransmitter-gated channel
Neuromuscular Transmission

- Presynaptic events
- Events in the synaptic cleft
- Post-synaptic events
Presynaptic Events

- Synthesis of ACh

Choline Acetyltransferase

Acetyl CoA + Choline $\rightarrow$ Acetylcholine
Presynaptic Events

- ACh packaged into vesicles in discrete units called quanta
  - Each quantum contains ~ 10,000 molecules of ACh
- Quanta are located in 3 separate stores
  - Primary store: ~1000 quanta available for immediate release
  - Secondary store: ~10,000 quanta that can resupply primary store after several seconds
  - Tertiary store: ~100,000 quanta distant from NMJ
Presynaptic Events

- Presynaptic nerve terminal lined with active zones which are specific sites on membrane where vesicles attach and release ACh into synaptic cleft
Pre-Synaptic Events

- AP invades and depolarizes nerve terminal
- Voltage gated Ca++ channels open, allowing influx of Ca++
- Ca-dependent binding of vesicles to terminal membrane occurs
  - Relatively slow, lasts 0.5msec (of total 0.75msec for NMJ transmission)
- Near-synchronous release of up to 200 quanta
  - Number of quanta released proportional to concentration of Ca++
Synaptic Events

- **Synaptic cleft**
  - Space between nerve terminal and depression in the postsynaptic membrane into which the terminal fits
  - Site of hydrolysis of ACh by acetylcholinesterase (AChE)
Post-synaptic Events

- **Post-synaptic membrane**
  - Region of muscle fiber membrane across from the nerve terminal, a.k.a. endplate
    - 1 endplate per fiber, number increases with reinnervation
  - Contains multiple infoldings called secondary clefts
    - Nicotinic ACh receptors concentrated on crests of folds
    - AChE concentrated in depths of clefts
  - ACh receptor is a transmembrane glycoprotein which binds 2 ACh molecules, opening a central channel in the receptor for a few msec, allowing Na+ to enter down its electrochemical gradient
NMJ Ultrastructure
Nicotinic ACh Receptor
Post-synaptic Events

- ACh diffuses across synaptic cleft and binds to ACh receptors, generating an end plate potential (EPP)
- If the EPP > threshold for generating an AP, all-or-none depolarization of the muscle membrane occurs
  - Threshold around 40-60 mV
Post-synaptic Events

- Propogated AP penetrates T tubule system, triggering muscle fiber contraction
- EPP terminated via hydrolysis of ACh by AChE within a few msec
Disorders of the NMJ

- Myasthenia gravis
- Congenital Myasthenic Syndromes
- Lambert-Eaton Myasthenic Syndrome
- Botulism
- Miscellaneous disorders of the neuromuscular junction
Myasthenia Gravis

- Incidence: 1-9 per million
  - F>M (7:3 in young age group, 1:1 in older)
  - F peak at ages 20-24 and 70-74 years
  - M peak at ages 30-34 and 70-74 years

- Prevalence: 25-142 per million

- 10% cases present in childhood
  (juvenile myasthenia)
MG

- Pathophysiology
  - In 85% patients with generalized MG and 50% patients with ocular MG, antibodies directed against ACh receptors
    - Binding antibodies- most common
    - Blocking antibodies
    - Modulating antibodies
  - MuSK antibodies
  - Other antibodies: LRP4, agrin
Pathophysiology

- In the case of antibodies to ACh receptors, damage to the NMJ occurs from:
  - Accelerated degradation of ACh receptors
  - Blocking active sites on ACh receptors
  - Damaging ACh receptors with the aid of complement
Thymic pathology

- 40-70% of patients with autoimmune MG have evidence of thymic hyperplasia
- 10-15% of patients with autoimmune MG have underlying thymoma
- 30% of patients with thymoma develop MG
MG

- Presenting Symptoms
  - Ocular: Ptosis, diplopia
  - Bulbar: Dysphagia, dysarthria, dysphonia, jaw fatigue
  - Respiratory: Dyspnea, orthopnea
  - Generalized: Neck, limb weakness
  - Distinctive feature is fluctuating nature of symptoms, producing a dynamic rather than static disorder
In the vast majority of patients (90%), ocular symptoms are first manifestation.

Generalization ultimately occurs in two-thirds of patients with OMG, the majority within 2 years.

In most patients, the severity of disease lessens with time and remissions are possible.
Exam

- Ocular signs
  - Ptosis, diplopia on testing of EOM, weakness of eye closure, over-contraction of frontalis

- Bulbar signs
  - Jaw weakness, facial diplegia, palatal weakness, tongue weakness

- Respiratory signs
  - Respiratory rate, use of accessory muscles, ease of speech

- Neck strength
- Limb strength
  - Examine for fatigability
MG

- Diagnostic Work-up
  - Antibody testing
    - ACh receptor antibodies in 85% GMG, 50% OMG
    - MuSK antibodies in roughly 10% GMG, rare OMG
  - Thyroid function studies
  - EMG and Nerve Conduction Studies
  - Evaluation for thymic pathology
    - CT or MRI of the chest
  - Edrophonium (Tensilon) test
  - Ice pack test
3 Hz Repetitive Nerve Stimulation

Single Fiber EMG
MG

- **Treatment**
  - Ocular vs. Generalized
  - Acetylcholinesterase inhibitors
  - Prednisone
  - Steroid-sparing agents
  - IVIg
  - Plasmapheresis
Treatment of Ocular MG

- Initially, pyridostigmine
- If symptoms refractory to pyridostigmine and impacting quality of life, prednisone
MG

- Anti-acetylcholinesterase medications
  - Most commonly used is pyridostigmine (Mestinon)
  - Transiently inhibits AChE from metabolizing ACh
  - Initiated at dose of 30-60mg q6h
  - Gradually titrated to effect, most adults requiring 60-120mg q4-6h
  - Doses exceeding 600mg/day typically ineffective and produce side effects
Treatment of Generalized MG

- Initial treatment with pyridostigmine and prednisone
- Subsequent treatment with “steroid sparing agent”
  - Azathioprine
  - Cyclosporine
  - Mycophenolate mofetil
  - Tacrolimus
  - IVIg
  - Eculizumab in severe cases
- Thymectomy if thymoma present or in young patients with thymic hyperplasia
Myasthenic Crisis

- Strictly defined as respiratory failure due to myasthenia gravis, though impending respiratory failure also qualifies.
- Causes: infection, illness, surgery, trauma, stress, medications.
- More commonly occur within 3 years of initial diagnosis of MG.
- Diagnosis:
  - Largely based on history and exam.
  - Assessment of pulmonary function (spirometry).
Myasthenic Crisis

- **Treatment**
  - Protection of airway
    - Endotracheal intubation and ventilation versus non-invasive positive pressure ventilation
  - Signs of impending respiratory failure:
    - Rapid progression of weakness
    - Neck flexor weakness
    - Inability to converse in complete sentences
    - Use of accessory muscles
    - Tachypnea
    - Spirometry: NIF < -30cc, FVC < 15cc/kg or declining trend in these parameters
Myasthenic Crisis

- **Treatment**
  - Directed treatment toward inciting event if identifiable (e.g. infection)
  - Prudent to hold anti-acetylcholinesterase drugs
  - Plasmapheresis
Medications that can worsen MG

- **Anesthetics**: Chloroprocaine, Diazepam, Ether, Halothane, Ketamine, Lidocaine
- **Neuromuscular blocking agents**: Propanidid, Procaine, **Botox**, Magnesium
- **Antibiotics**: Aminoglycosides, Amikacin, Gentamicin, Kanamycin, Neomycin, Netilmicin, Paromomycin, Spectinomycin, Streptomycin, Tobramycin, **Fluoroquinolones**, Ampicillin, Clarithromycin, Clindamycin, Colistin, Erythromycin, Lincomycin, Quinine, Telithromycin, Tetracyclines
- **Anticonvulsants**: Gabapentin, Phenytoin, Trimethadione
- **Antipsychotics**: Chlorpromazine, Lithium, Phenothiazines
- **Antirheumatic drugs**: Chloroquine, **Penicillamine**
- **Cardiovascular drugs**: Beta blockers, Bretylium, Procainamide, Propafenone, Quinidine, calcium channel blockers
- **Glucocorticoids**
- **Ophthalmologic drugs**: Betaxolol, Echothiophate, Timolol, Tropicamide, Proparacaine
- **Other drugs**: Anticholinergics, Carnitine, Cholinesterase inhibitors, Deferoxamine, Diuretics, Emetine (Ipecac syrup), Interferon alpha, Iodinated contrast agents Oxytocin, Antiretroviral protease inhibitors, Statins, Thyroxine
- **Narcotics**
- **Oral contraceptives**
Congenital Myasthenic Syndromes

- **Presynaptic disorders**
  - Choline acetyltransferase deficiency
  - Paucity of synaptic vesicles

- **Synaptic disorders**
  - End plate AChE deficiency

- **Postsynaptic disorders**
  - Primary kinetic defect +/- AChR deficiency
  - Primary AChR deficiency +/- kinetic defect
  - Rapsyn deficiency
  - Sodium channel myasthenia
  - Plectin deficiency
  - Dok-7 myasthenia
Lambert-Eaton Myasthenic Syndrome

- Rare

- Presentation
  - Patients typically complain of weakness and easy fatigability, predominantly of proximal lower extremities
  - Oculobulbar symptoms less common than in MG
  - Cholinergic dysautonomia
LEMS

Exam

- Signs of cholinergic dysautonomia
- Proximal muscle weakness, improved with repetitive testing (facilitation)
- Hyporeflexia, improved with facilitation
LEMS

■ Pathophysiology

- Antibodies directed against P/Q voltage-gated calcium channels on presynaptic membrane at both NMJ and preganglionic parasympathetic nerve terminals
LEMS

- Roughly two-thirds of cases associated with underlying malignancy
  - Most common underlying malignancy is SCLC (90%, others include lymphoproliferative disorders, breast, ovarian, and pancreatic ca)
- Diagnosis typically precedes that of malignancy by ~10 months
LEMS

- Diagnostic work-up
  - Antibody testing
    - 85-90% of pts have anti-P/Q voltage-gated Ca channel antibodies (both paraneoplastic and non-paraneoplastic)
    - ~10% of pts also have anti-ACh R antibodies
  - Electrodiagnostic studies
  - Evaluation for malignancy
    - CT torso
LEMS

Pre- and post-tetanic stimulation (10 seconds of maximal voluntary contraction)

50 Hz RNS
LEMS

- Treatment
  - Of malignancy- patients may improve
  - Anti-acetylcholinesterase drugs may produce a modest effect (variable)
  - 3,4 diaminopyridine
  - Immunosuppression (steroids, IVIg, plasmapheresis)
Botulism

- Caused by toxin of *Clostridium botulinum*
  - Gram positive, rod-shaped, obligate anaerobe
  - A, B, E strains of toxin most common
- Can be acquired via several routes:
  - Wound
  - Food borne
  - Infantile
  - Hidden (suspected gastrointestinal)
  - Inhalational
Botulism

- **Pathophysiology**
  - Neurotoxins produced by C. botulinum degrade proteins necessary for docking and fusion of ACh vesicles to the synaptic membrane, thereby preventing release into the synaptic cleft.
Botulism

- **Presentation**
  - Neurologic: Dysphagia, xerostomia, diplopia, dysarthria begin acutely and progress over 12-36 hours with rostral to caudal progression of weakness eventually involving limbs and/or respiratory muscles
  - Gastrointestinal: Nausea, vomiting, diarrhea followed by constipation, abdominal cramps
  - Anxiety
Botulism

- **Exam**
  - Ptosis, ophthalmoplegia, facial diplegia, palatal and tongue weakness
  - Limb weakness and hypo- to areflexia
  - Evaluation of respiratory function
  - Signs of dysautonomia: e.g. poorly reactive pupillary light response, bradycardia
Botulism

- Differential Diagnosis
  - Myasthenia gravis
  - Guillain-Barre syndrome
  - Tick paralysis
  - Poliomyelitis
  - LEMS
  - Heavy metal intoxication
  - Brainstem stroke
Botulism

- Diagnostic work-up
  - Toxin
    - Serum in foodborne
    - Stool in infantile
    - Wound scrapings in wound
  - EMG/NCS
Botulism

- **Treatment**
  - Supportive care
    - Respiratory monitoring, intubation as necessary
    - Gastrointestinal symptoms
  - Anti-toxin
    - Equine serum trivalent botulism antitoxin (A, B, E) is available in the United States through State Health Departments or the CDC
    - Early treatment
  - Antibiotics
    - Unproven but often given for wound botulism
Botulism

- Most patients require hospitalization for 1 to 3 months for supportive care
- Mortality rate ~5%
Other Causes of Neuromuscular Junction Dysfunction

- Drug-induced MG (penicillamine, amiodarone)
- Aminoglycoside antibiotics
- Hypermagnesemia
- Envenomations (various snakes, scorpions, spiders, cobras, kraits)
- Certain forms of tick paralysis
- Agents designed for chemical warfare
- Prolonged neuromuscular blockade (curare-like agents in the critically ill)
Questions?

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