Disorders of Neuromuscular Transmission

Zakia Bell, M.D.
Associate Professor of Neurology and
Physical Medicine & Rehabilitation
Virginia Commonwealth University
School of Medicine

Disorders of Neuromuscular Transmission

- Stereotyped sequence of events
  - propagation of an action potential distally along peripheral motor nerve axons
  - action potential invasion of the nerve terminal
  - calcium entry into the presynaptic zone of the nerve terminal
  - migration of acetylcholine packets to the active zone of the nerve terminal
  - acetylcholine quantal release

- diffusion of acetylcholine across the synaptic cleft
- binding of acetylcholine molecules to the post synaptic muscle end plate receptor zone
- opening of sodium channels
- sodium influx into muscle resulting in end plate potentials
- achieving threshold depolarization with generation of muscle fiber action potential

- propagation of the muscle action potential along the muscle membrane and into the transverse tubular system
- sarcoplasmic reticulum release of calcium
- inhibition of tropomysosin-troponin complex
- actin and myosin interaction
- muscle contraction

- Efficient process occurs up to 50 times per second
- Every time a nerve depolarizes
  - between 2 and 5 times as much acetylcholine is released
  - safety factor
    • diseases which alter the safety factor result in disorders of neuromuscular transmission

Neuromuscular Transmission
Disorders of Neuromuscular Transmission

- Presynaptic disorders
- Postsynaptic disorders
  - myasthenias
  - organophosphate poisoning

Myasthenia Gravis

- Paradigm disorder of neuromuscular transmission
- Reduction or loss of receptor sites for acetylcholine binding on the post synaptic muscle membrane
- Autoimmune disease
- Reduced probability of acetylcholine-receptor combination
- Resultant failure of neuromuscular transmission
  - results in weakness and or fatigability of the contracting muscle

Myasthenia Gravis

- Diagnosis made by history of weakness and fatigability
  - bulbar and proximal limb muscles most commonly affected
- Tensilon testing (edrophonium) temporarily inactivates cholinesterase allowing increased acetylcholine at the synaptic cleft and may temporarily improve strength

Repetitive Nerve Stimulation: Myasthenia Gravis
Myasthenia Gravis

- EMG testing produces a decremental response to low rates of nerve stimulation
- Determination of pathologic levels of serum acetylcholine receptor antibodies
  - sensitive and specific for autoimmune myasthenia gravis

Other Forms of Myasthenia Gravis

- Congenital and familial
- Heterogeneous group of disorders
  - not due humorally modulated autoimmunity
    - reflect structural and biochemical abnormalities of neuromuscular transmission

Disorders of Neuromuscular Transmission

- Presynaptic
  - Lambert-Eaton syndrome
  - antibiotic poisoning
  - hypermagnesemia
  - botulinum poisoning

Presynaptic Disorders in Neuromuscular Transmission

- Result from impaired quantal release of acetylcholine from the presynaptic nerve terminal
- Tetanic contraction either volitional exercise or in response to high rates of electrical stimulation of nerve improves the release of acetylcholine by increasing calcium through the presynaptic membrane
Presynaptic Disorders in Neuromuscular Transmission

- Disorders affecting presynaptic acetylcholine release
  - Myasthenic syndrome (Lambert-Eaton):
    - commonly associated with oat cell carcinoma of the lung in the middle aged
  - Botulinum poisoning
  - Poisoning with aminoglycoside antibiotics
  - hypermagnesemia

Lambert-Eaton Syndrome

- Males affected more than females
- Younger onset not associated with neoplasm
- Clinical features
  - weakness more proximal with legs affected more
  - cancer associated, usually lung

Lambert-Eaton Syndrome

- Clinical
  - weakness precedes cancer in more than 80%
  - improves after brief sustained contraction
  - autonomic neuropathy

Lambert-Eaton Syndrome

- Electrophysiology
  - increment after rapid repetitive nerve stim
  - P type calcium channels usually involved
  - antibodies to calcium channels

Lambert-Eaton Syndrome

- Treatment
  - treating underlying neoplasm if present
  - immunosuppressive drugs
  - 3,4 diaminopyridine
    - potassium channel blocker
    - helps to maintain depolarization by preventing repolarization
    - allow more calcium to enter nerve terminal to release more acetylcholine

Repetitive Nerve Stimulation: Lambert-Eaton