Lecture 19 Channelopathies: Myotonia and Periodic Paralysis
March 24, 2017
Summary

• Overview and classification
  – channelopathies
    • myotonia
    • periodic paralysis (PP)

• Clinical findings

• Review
  – Ion Channels
  – Normal muscle physiology
  – Abnormal muscle physiology:
    – What accounts for the different channelopathies?

• Electrophysiological recordings in myotonia and PP
  – single channel
  – multiple channels
  – conductance
Classification

• Myotonic diseases belong to a class of disorders known as **channelopathies**
  – over 20 different channelopathies have been described
  – channelopathies affect a wide variety of cell types, manifesting as episodic disorders of the brain (e.g., epilepsy), heart (e.g., cardiac arrhythmias) kidney and skeletal muscle (e.g., myotonia, periodic paralysis)
  – due to mutations in voltage-gated channels

• In skeletal muscle, channelopathies are associated primarily with mutations in voltage-gated Na\(^+\) and Cl\(^-\) channels, and to a lesser extent K\(^+\) and Ca\(^{2+}\)
  – Result: a continuum of disorders ranging from those characterized by **hypoexcitability** (manifests as periodic paralysis) to **hyperexcitability** (manifests as myotonia)
Classification of Channelopathies

• General scheme for classification of channelopathies is as follows:

- Superfamily Classification
- Tissue Affected
- Disorder Subtypes
Clinical Findings – Myotonia

- Myotonic disorders are diseases characterized by myotonia
  - characterized by an inability to quickly relax muscle after a voluntary contraction, percussion or electrical stimulation
  - may be restricted to certain muscles (e.g., intrinsic hand muscles) or occur as a generalized condition
  - myotonic dystrophy (myotonia with progressive muscle degeneration) and myotonia congenita are two relatively common forms of myotonic disorders
  - may be inherited or acquired
Clinical Findings – Myotonia

• Clinical findings depend on disease subtype
  – e.g., *myotonic dystrophy* includes cataracts, frontal baldness, reduced bulk of lower facial muscles (buccinator, etc.), drooping eyes (ptosis), weak smile

• EMG abnormalities

• Temperature sensitivity depends on subtype
  – Myotonia congenita
    • minimal sensitivity to cold
    • symptoms improved by “warming up”
  – Paramyotonia
    • often dramatic sensitivity to cold
    • no improvement with warmup

*FIGURE 4. Myotonic discharge. EMG of typical myotonic discharge demonstrating waxing and waning of both amplitude and frequency.*
Clinical Findings – Myotonia

- Regardless of subtype, myotonic disorders have as their central feature **myotonia**
Clinical aspects

• Slight myotonia – usually asymptomatic
• Sometimes embarrassing
• May still be able to exercise: there can be ‘warm up’ where the myotonia is less evident with repetition
• Can be a problem in cold weather, lose balance and fall
• Stiffness and cramping
• See ‘Fainting Goats’ video (U tube)
Periodic Paralysis (PP)

- A group of muscle disorders with episodic weakness
- The reason that the PP are associated with myotonia is because PP are also due to a channelopathy resulting in weakness
- The general mechanism of periodic paralysis is sarcoplasmic depolarization resulting in the inexcitability of Na+ channels (or other channels)
ION CHANNELS IN MUSCLE

Na⁺ Channel
Cl⁻ channel
K⁺ channel
Inward rectifier
Ca²⁺

Figure 1
Propagation of excitation in skeletal muscle and channelopathies of electrical excitability. This schematic representation of a neuromuscular junction and muscle fiber shows the sequence of electrical events that couples motor neuron firing to myoplasmic Ca²⁺ release and the ion channels for which mutations have
Clinical spectrum of the nondystrophic myotonias and periodic paralyses. Myotonia predominates in disorders further to the left in this spectrum, whereas periodic paralysis is the major symptom for those toward the right. The underlying molecular genetic defects in each of these disorders are mutations in voltage-gated ion channel genes (middle row). Insets below show an electromyographic recording of a
Periodic Paralysis – Classification and Clinical Findings

• Different forms of Periodic Paralysis (PP) are distinguished by the serum K+ level during the attacks
  – e.g., hyperkalemic PP, normokalemic PP, hypokalemic PP
    • hyperkalemic variant has an earlier onset and more frequent attacks, yet attacks are much shorter and milder than in the hypokalemic form
    • Intake of K+ and glucose have opposite effects in the two disorders:
      – Hyperkalemic PP: K+ triggers attack; glucose intake is a remedy
      – Hypokalemic PP: glucose provokes attack; K+ intake is a remedy
      – Reason is that insulin causes shift of K+ into cells (decreases plasma K concentration)

• Usually presents in the first or second decade of life with attacks of trunk and leg \textit{paresis} during sleep or shortly after awakening
  – mild to moderate degree of muscular weakness
  – symptoms may persist for hours to days and generally are precipitated by exercise
Clinical findings - periodic paralysis

- Usually normal usually
- However, when triggered get weakness without sensory findings or pain that comes on over hours; usually proximal weakness and symmetric.
- Usually autosomal dominant
- Usually bulbar (brain stem innervated muscles) and thoracic muscles OK
- Can be triggered by rest after exercise
Classification Myotonia vs. PP

• The distinction between myotonia and periodic paralysis is not absolute

<table>
<thead>
<tr>
<th>Hypoexcitability</th>
<th>Hyperexcitability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periodic paralysis</td>
<td>Myotonia</td>
</tr>
<tr>
<td>Facial features EKG (Andersen-Tawil)</td>
<td>Hypokalaemic</td>
</tr>
</tbody>
</table>

Functional electromyography

- Potassium channel KCNJ2
- Calcium channel
- Chloride channel
- Sodium channel
Normal Muscle Physiology – A Review

- Motorneuron activity is transferred to skeletal muscle across the NMJ, generating an action potential in the muscle that propagates along the surface membrane including the transverse tubular system (TTS)
  - The upstroke of the action potential is mediated by opening of the voltage gated Na+ channels that elicit a Na+ inward current with rapid activation kinetics.
  - Repolarization of the membrane by rapid Na+ channel inactivation is additionally supported by opening of K+ channels that mediate an outward K+ current.
  - Buffering of undershoot is achieved by a high Cl– conductance near the resting potential resulting from the homodimeric Cl– channels.
Normal Muscle Physiology – A Review

• At specialized junctions in the TTS, the signal is transmitted from the outer membrane to the inside causing the release of Ca2+ ions from the SR
  – This in turn activates the contractile apparatus, a process called **excitation-contraction coupling**.

  • Two main Ca2+ channels are involved in this process: the voltage gated pentameric dihydropyridine receptor located in the TTS and the homotetrameric ryanodine receptor of the SR. The voltage gated Ca2+ channel is activated by membrane depolarization → this then activates the ryanodine receptor by direct protein/protein interaction which in turn releases Ca2+ into the cytosol → force generation → muscle contraction.
Muscle is different from nerve

• Recall that muscle has a somewhat more hyperpolarized resting potential than neurons ( -83 mV at 4mM K+)

• There are some different conductances in muscle than nerve, for instance there is a high chloride conductance in muscle at rest.

• There is also a large inward rectifier K+ current (Kir), this is a current that causes K+ INflux when the myocyte is hyperpolarized. However, curiously the current is dependent on [K] extracellular and this can lead to ‘unusual’ non-Nernst behaviour. Remember the Nernst equation only works if the channels are continually open.
Abnormal Muscle Physiology – Basic Premise

• Thus, given the role of ion channels in the excitation of the muscle membrane and eventual muscle contraction, mutations to these channels would naturally be expected to alter excitability of the muscle membrane and thus muscle tone and contractile characteristics.
  
  – If the sarcolemma responds with multiple action potentials to a single stimulus at the NMJ, prolonged contractions will occur. Conversely, if the sarcolemma fails to respond to a postsynaptic potential of normal size, weakness of the muscle will occur.
What accounts for the different channelopathies?

- The various types of skeletal muscle channelopathies result from mutations to different components of ion channels
  - Different mutation in ion channel = different location in receptor structure = different effects on receptor function (e.g., inactivation) = different electrophysiological features = different diseases
- There are various forms of Na+ channel inactivation

Where do you suppose the inactivation gate is?
Skeletal muscle sodium channel Structure

Fig. 1 Membrane topology model of the voltage-gated sodium channel of skeletal muscle. The α subunit functions as an ion-conducting channel and consists of four highly homologous domains (repeats I–IV) containing six transmembrane segments each (S1–S6). The S6 transmembrane segments and the S5–S6 loops form the ion selective pore, and the S4 segments contain positively charged residues conferring voltage dependence to the protein. The repeats are connected by intracellular loops; one of them, the III–IV linker, contains the supposed inactivation particle of the channel. When inserted in the membrane, the four repeats of the protein fold to generate a central pore as schematically indicated on the right-hand bottom of the figure. The different symbols used for the known mutations leading to potassium-aggravated myotonia, paramyotonia congenita or two types of periodic paralysis are explained bottom left-hand. Conventional 1-letter abbreviations were used for replaced amino acids.
Normal Receptor Function – Sodium

• The Na⁺ channel is thought to have 3 distinct possible configurations:
  – open state
    • occurs upon membrane depolarization → outward movement of voltage sensor upon depolarization results in both opening of pore and exposure of a docking site for inactivation gate
  – inactivated state
    • fast inactivated state
      – occurs after open state
      – channel very rarely reopens in this state
    • slow inactivated state
  – resting (closed) state
    • activation of channel is once again possible in this state
General structure of a voltage-dependent ion channel

Four subunits, each of which has 6 transmembrane spanning segments

K et al., 5-7
Receptor Structure – Calcium

Fig. 2 Subunits of the voltage-gated calcium channel. The α1 subunit resembles α of the sodium channel however the function of the various parts, e.g. the III–IV linker, may not be the same. α2/δ, β1 to β4, and γ are auxiliary subunits. Mutations in the α15 subunit shown here of the skeletal muscle L-type calcium channel (= dihydropyridine receptor, DHPR) have been described for man (HypoPP, MHS5) and mice (mdg). Conventional 1-letter abbreviations are used for the replaced amino acids. The symbols indicate the diseases as explained at the bottom of the left-hand side.
Normal Receptor Function – Calcium

• Via excitation-contraction (EC) coupling, voltage gated calcium channels are closely linked to SR calcium release, force generation and eventual muscle contraction
  – mutations in respective genes are associated with hypokalemic periodic paralysis
Receptor Structure – Chloride

Fig. 4 Membrane topology model of the skeletal muscle chloride channel monomer, CIC-1, modified after [16]. The functional channel is a homodimer. The different symbols used for the known mutations leading to dominant Thomsen-type myotonia and recessive Becker-type myotonia are explained on the left-hand bottom. Conventional 1-letter abbreviations were used for replaced amino acids.
Electrophysiological Changes

- Single channel current recordings show disrupted fast inactivation with bursts of openings (downward deflections) in a hyperkalemic PP mutant channel.
- The mutant channels **do** inactivate for the majority of trials but intermittent bursts cause a small, yet persistent, Na⁺ current.
  - only a few mutant channels are necessary to cause major, clinical effects
Mutant Na channels

Mutant: openings are prolonged
Electrophysiological Changes

- Recordings of aggregate (i.e., multiple summed) currents show changes in the open duration of Na+ channels
  - Mutant Na+ channels remain open for longer than WT Na+ channels
    - results in more current passed through channel
    - due to slowed rate of fast inactivation of Na+ channels
Shifts in Both Activation and Inactivation Affect Excitability

• Shifts in activation affect excitability:
  • Hyperpolarized shift in $V_{1/2} = \text{increased excitability}$ because channels open at lower voltages, so increased probability of activation
  • Depolarized shift in $V_{1/2} = \text{decrease excitability}$ because channels open at more depolarized voltages, so decreased probability of activation

• Shifts in inactivation affect excitability:
  • Hyperpolarized shift in $V_{1/2} = \text{increased excitability}$ because fewer channels are inactivated
  • Depolarized shift in $V_{1/2} = \text{decrease excitability}$ because more channels are inactivated
Electrophysiological Changes

- Recovery time ($T_{\text{recovery}}$) is measured as the relative current available after a brief return to resting potential (-80mV, in this case)
  - $T_{\text{recovery}}$ is much reduced in mutant myotonic channels
    - due to channels leaving the fast inactivated state too quickly
    - leads to shortened absolute and refractory periods as well as higher frequency firing.

![Diagram](image-url)
PP – An integrative mechanism

EXPLANATION FOR PARALYTIC ATTACKS IN HYPERKALEMIC PERIODIC PARALYSIS PATIENTS

- [K+] intake or exercise followed by rest
- small increase of extracellular [K+]
- slight membrane depolarization
- opening of Na+ channels but also switch abnormal Na+ channels to non-inactivating mode
- persistent inward Na+ current
- sustained depolarization of cell membrane
  - efflux of K+
  - increase of [K+]o
  - inactivation of normal Na+ channels
  - loss of electrical excitability
  - paralytic attack
The role of the T-tubular system

The point of this slide is that K+ efflux occurs in muscle including the T-tubule system; as the T-tubules are a small space; K+ can build up, high intratubular K+ can then lead to a membrane depolarization. This can be blocked by substances that cause ‘de-tubulation’, they destroy the T-tubules.
Action potential in muscle

- End plate potential (Ach)
- Na+ channels open
- Membrane depolarizes
- Depolarization reaches threshold (Na+ conductances bring potential to greater value than gCl- and gK+
- Na+ channels are open, membrane approaches Erev Na+; membrane depolarization triggers Na+ channels to undergo conformational change from open to fast inactivated state, delayed rectifier channels open
- Emem moves toward Erev K
- Na+ channels in fast inactivated state (absolute refractory period)
- Na+ channels move from inactivated state to closed state (relative refractory period)
- If Na+ channels do not inactivate with the right time course-muscle can remain persistently depolarized
- Action potential invades transverse tubules
- K+ efflux into T-tubules
- Changes in E memb in T-tubules –plasmalemmal junction –because of an increase in intratubular K+ -E memb depolarizes
- Membrane of t-tubule can remain depolarized. Need Na+ K+ pump to remove K+ from tubule, but pump slow. T-tubules need high chloride to hyperpolarize
- T-tubules produce depolarizing current which can trigger subsequent action potentials. If you remove t-tubules – you inhibit muscle membrane from generating a string of action potentials in response to a stimulus