Myotonia Congenita

Why does it happen?
What can we do about it?

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I have stiff legs...

Muscular physique

- Tripping and falling without counterbalancing
- "Your dad must be Hercules"
- Many doctors, EEGs, EKGs:
  - "drink milk & go jogging"
  - "just do your best"
  - "in case of a fire, I bet you can run"
- "Rebel student": gets up provocatively slow when called to the board

Muscle doesn’t work
- "I can’t do that"

Conflict

What am I doing wrong?

What body position, what food, what action stops the cramping?

Endless wondering:
Overview

I. Myotonia History
   Brief review of the contributions of Thomsen, Becker, and modern scientists.

II. Myotonia Physiology: “What am I doing wrong?” (Nothing!)
   a) How cells talk to each other: Ion channels
   b) Animal models

III. Myotonia Therapy
   a) Established: Mexiletine, quinine, phenytoin…
   b) New: Lacosamide
A brief history on myotonia research

1830 – Charles Bell

“... a gentleman capable of great bodily exertion, on going to hand a lady to the dining-room, will stagger like a drunken man; and in the streets any sudden noise, or occasion of getting quickly out of the way, will cause him to fall down...”

1874 – Ernst von Leyden

“The musculature... demonstrated an athletic development.... pronounced stiffness... muscle will not promptly respond to willfully initiated movement.... If only mildly flexed, the fingers can be rapidly extended. However, if the fist is tightly closed, it is impossible for him to extend the fingers immediately... overcome a considerable resistance. After executing this maneuver several times, however, the extension now goes smoothly....
A brief history on myotonia research

1876 – Asmus Julius Thomas Thomsen
Aflicted physician writes landmark account on his family, after his son was accused of being a simulant trying to evade military service. Thomsen recognizes it as a heritable disorder, documenting it over 5 generations with 20 individuals.

1881 – Ernst von Strümpell
Coins the term “myotonia”

1883 – Karl Westphal
Suggests “Thomsen's disease”
A brief history on myotonia research

1961 – Peter Emil Becker
German neurologist specializing in muscle disorders recognizes that, aside from Thomsen’s disease, there is a second type of myotonia with a distinct inheritance patter (which became “Becker’s disease”)

1970s Reinhardt Rüdel, Shirley Bryant, Allen Bretag, Robert Barchi
1980s Harald Jokusch, Frank Lehmann-Horn
1990s Kenneth Ricker, Manuela Koch, Al George
2000s Colding-Jørgensen, Dunø, Hanna, Trivedi, Barohn, Cannon
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Myotonia: an error in life’s building instructions

Myotonia is the result of DNA errors that provide incorrect building instructions for proteins. One error in of our 3.3 billion DNA letters is enough...

Healthy: “Connect Part A to B and then attach C”
Mutant: (C) ”Onnectp Arta T ob A ndt hena ttachc”

The mutation may
• improve the quality of life (Darwin)
• have no consequence
• cause disease (myotonia 10 in 100,000)
Neurons and muscle cells communicate using electricity. In myotonia, communication components that allow ions to flow in and out of muscle cells, so-called ion channels, are broken or don’t work properly.

**What are ion channels?**

Ion channels allow for...

- Na\(^{+}\) currents
- K\(^{+}\) currents
- Ca\(^{2+}\) currents
- Cl\(^{-}\) currents
Myotonia at the cellular level

1. Na⁺/K⁺ ATP generates $E_{\text{mem}}$ (mostly via $P_K$)
2. AP: Na⁺ in/K⁺ out; note the t-tubular $[K^+]_o$ (confinement!), but CIC-1 "clamps" $E_{\text{mem}}$ close to $E_{Cl}$
3. CIC-1 missing, hence $E_{\text{mem}} = \text{abnorm } E_K$ ⇒ excessive excitation

$E_{\text{mem}} \approx E_K$ (and $E_{Cl}$)

myo- (Greek: muscle), -tonus (Latin: tension)
Myotonia – how does it look like?

- **Presentation:**
  - “cramping” (inability to relax muscle)
  - repeated motion provides relief (“warm-up phenomenon”)
  - muscular appearance
  - temporary weakness

- **Myotonic disorders:**
  - “Stand-alone”
    - Thomsen’s (dominant inheritance)
    - Becker’s (recessive inheritance)
  - As part of a more complex presentation
    - myotonic dystrophy
    - paramyotonia congenita
    - K⁺-aggravated myotonia
    - periodic paralysis

(P.E. Becker et al. eds., *Myotonia congenita and [..] in: Topics in Human Genetics, Thieme*)
Willing myotonia to end?

“There is neither disease of mind nor of bodily organs; the corporeal frame is perfect; the nerves and muscles are capable of their functions and proper adjustments; the defect is in the imperfect exercise of the will…”
(Bell, 1830)

“The seat of the evil is certainly to be sought within the cerebrospinal system or the brain itself in that part from which willfulness originates. [The will] does not achieve contact in an appropriate fashion with the organs through the nerves facilitating movement....”
(Thomsen, 1876)

Is there a way to stop myotonia by will?
Myotonia relief... just try harder?

Brain → Neuron → Muscle

“Contract!”

“Relax!”

Stopping myotonic cramping by will is **physiologically impossible!**
The mental burden of myotonia

"...affected my psyche very badly and caused a great irritability...." (Thomsen, 1876)

"This distressing condition was accompanied by moods of depression and an extremely labile personality.... Her stiffness has made her the object of ridicule at school.” (Isaacs, 1959)

“While in the Army, he was often accused of malingering at the beginning of calisthenic periods and marches, because he was unable to make fast movements without a prior limbering” (Freeble, 1949)
Myotonia models

- Genetic:
  - YouTube’s “Fainting goats”, dogs, cats, frogs, etc.
  - myotonic mice in the lab

- Induced:
  - 9-anthracene carboxylic acid (9-AC)
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Do not try this at home!

Self medication, especially with myotonia, can be fatal. Myotonia drugs target mechanisms that are very similar in muscle, heart, and brain.

Overdosing will lead liver damage, hearing and vision problems, seizures, cardiac arrest, and possibly death!
The crux with antimyotonic drug development

- Strong day-to-day variance for myotonia in the same patient
- Influence of the patient’s subconscious effort to hide the disorder
- What works in one patient, may have no affect in another
- Muscle exercise history influences effect (e.g., intense workout)

How can we measure an antimyotonic effect and how do we ensure safety?
Electrophysiology

Ion channel mutants:
Do they react more slowly or faster?
Do they open and close properly?
Do they conduct more or less current?

In-vitro pharmacology:
Can we rectify any defects?

In-vivo pharmacology:
Does a mutant mouse fare better with candidate drug?
Mexiletine: The current “first choice”

- quinine
- tocainide
- carbamazepine
- mexiletine
- lacosamide
- ranolazine

The challenge:
Unwanted effects in brain and heart!
Summary

1. Myotonia refers to a muscle’s inability to relax. Influencing the same by will is not possible.

2. Drug development challenge: suppress only the myotonic reaction but leave normal function intact.

3. Several new approaches are currently being tested that seek to target only myotonia without producing unwanted effects.
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**Na\textsubscript{v} channel electrophysiology**

**Pipette**
- NaF (10 mM)
- CsF (110 mM)
- CsCl (20 mM)
- EGTA (2 mM)
- HEPES (10 mM)

**Bath**
- NaCl (145 mM)
- KCl (4 mM)
- CaCl\textsubscript{2} (1.8 mM)
- MgCl\textsubscript{2} (1 mM)
- HEPES (10 mM)

**Conditions**
- whole-cell patch clamping
- room temperature
- \(N \geq 7\) for all experiments

pH 7.35, 310 mOsm/kg
Cl⁻ channel myotonia

CIC-1 factoids

- Family: CIC-1...7, CIC-Ka, CIC-Kb
- Pathology: myotonia congenita (130+ mutations)
- Gene: CLCN1 (7q35)
- Size: 919 aa (110 kDa)
- Topology: 13 TM
- Stoichiometry: dimer
- Activation: voltage (open at rest)
- Distribution: skeletal muscle (some in glia)

(Nature 415: 287, Physiol Rev 82: 503)
Chloride channel myotonia

CIC-1 factoids

- **family:** CIC-1...7, CIC-Ka, CIC-Kb
- **pathology:** myotonia congenita (130+ mutations)
- **gene:** *CLCN1* (7q35)
- **size:** 919 aa (110 kDa)
- **topology:** 13 TM
- **stoichiometry:** dimer
- **activation:** voltage (open at rest)
- **distribution:** skeletal muscle (some in glia)

*(Nature 415: 287, Physiol Rev 82: 503)*
Sodium channel myotonia

**Na_v channel factoids**
- **family:** Na_v1.1 – Na_v1.9, Na_v2.1
- **pathology:** epilepsy, erythermalgia, myotonic disorders, arrhythmias (1000+ mutations)
- **genes:** SCN1A – SCN11A
- **size:** approx. 2000 AA
- **topology:** 4 x 6 TM
- **stoichiometry:** α + β(s)
- **activation:** voltage (opens with depolarization)
- **distribution:** excitable tissues

(T.L. Klassen, University of Columbia)
Ion channels... because oil and water don’t mix!

- phospholipids
- non-polar ⇒ hydrophobic
- intermolecular forces: *van der Waals*

- dipoles
- polar ⇒ hydrophilic
- intermolecular forces: *hydrogen bonds*

**Oil**
- phospholipids
- non-polar ⇒ hydrophobic
- intermolecular forces: *van der Waals*

**Water**
- dipoles
- polar ⇒ hydrophilic
- intermolecular forces: *hydrogen bonds*

**Micelle**

**Lipid bilayer**
Ion channels... because oil and water don’t mix!

- $K^+$ surrounded by hydration shell
- $K^+$ surrounded by “pseudo” hydration shell of the channel
- $K^+$ surrounded by hydration shell
- Energy state within the channel approximates the hydration shell of water
The $\text{Na}_v$ family - Structure

$\alpha$ subunits: $\text{Na}_v1.1$ – 1.9

Subunit-specific characteristics:
> biophysical profile
> expression pattern
$> \alpha\beta$ complexing

$\rightarrow$ tissue-specific function

$\beta$ subunits: $\beta_1$ - $\beta_4$
Na\textsubscript{v} 1.4 channelopathy phenotypes

1. Na\textsuperscript{+} channel myotonias (SCM)
   - m. fluctuans
   - m. permanens
   - K\textsuperscript{+}-aggravated m.
   - etc.
   \quad \text{similar to “classic” CIC-1 linked congenital myotonia: patient has \textit{muscle cramps} upon starting a new movement; cramps disappear with repetition: “\textit{warm-up phenomenon}”}

2. Paramyotonia congenita (PMC or Eulenburg’s)
   - paradoxical myotonia, exacerbated by cold
   - recurrent attacks of weakness

3. Hyper-/Hypokalemic periodic paralysis (hyper/hypoKPP)
   - paramyotonia-like phenotype with abnormal serum K\textsuperscript{+} levels
   - genetic modification $\Rightarrow$ diverse phenotype

4. Congenital myasthenic syndrome
Na\textsubscript{v}1.4 mutations (select few...)

G.O.F. $\Rightarrow$ SCM, PMC, hyperKPP
L.O.F. $\Rightarrow$ hypoKPP, CMS
Na\textsubscript{v} channel isoforms & expression

(Goldin et al., Neuron 28:365, 2000)
**$\text{Na}_\text{v}$ channel gating**

- **Out**
  - Resting
  - Slow-inactivated
  - Fast-inactivated

- **In**
  - Na$^+$

- **Na$^+$**
  - Active