Muscular Channelopathies
Periodic Paralysis

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## Periodic Paralysis

<table>
<thead>
<tr>
<th></th>
<th>hypoPP</th>
<th>Thyreotoxic</th>
<th>hyperPP</th>
<th>ATS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at onset</strong></td>
<td>&lt; 20 ys</td>
<td>&gt; 20 ys</td>
<td>&lt; 10 ys</td>
<td>&lt; 20 ys</td>
</tr>
<tr>
<td><strong>Attack frequency</strong></td>
<td>Infrequent</td>
<td>Infrequent</td>
<td>Frequent (several times a day)</td>
<td>monthly</td>
</tr>
<tr>
<td><strong>Attack duration</strong></td>
<td>Hours to days</td>
<td>Hours to days</td>
<td>Min to hours</td>
<td>hours</td>
</tr>
<tr>
<td><strong>Precipitants</strong></td>
<td>Exercise Carbohydrate load Stress</td>
<td>Exercise Carbohydrate load Stress</td>
<td>Exercise Fasting Stress K⁺-rich food</td>
<td>Rest after exercise</td>
</tr>
<tr>
<td><strong>K⁺ during attack</strong></td>
<td>Low</td>
<td>Low</td>
<td>Normal or elevated</td>
<td>Low, normal or elevated</td>
</tr>
<tr>
<td><strong>Associated features</strong></td>
<td>Later onset myopathy</td>
<td>Thyreotoxicosis Low TSH High T3, T4</td>
<td>Myotonia (clinical, EMG) Later onset myopathy</td>
<td>Dysmorphic features Ventricular tachycardia Long QT</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>AD Inherited defect Ca²⁺-channel or Na⁺-channel on muscle membrane</td>
<td>Thyreotoxicosis K⁺ conductance ↓ (mutation Kir 2.6)</td>
<td>AD Inherited defect Na⁺-channel on muscle membrane</td>
<td>AD inherited defect on inward rectifier K⁺-channel</td>
</tr>
<tr>
<td><strong>Penetrance</strong></td>
<td>Nonpenetrance common (women)</td>
<td></td>
<td>High</td>
<td>Nonpenetration and incomplete penetrance common</td>
</tr>
<tr>
<td><strong>Epidemiology</strong></td>
<td>Men more affected</td>
<td>Highest incidence in Asian men</td>
<td>Sexes equally affected</td>
<td>Marked intrafamiliar phenotypic variation</td>
</tr>
<tr>
<td><strong>Preventive TX</strong></td>
<td>Carboanhydrase inhibitors K⁺-sparing diuretics</td>
<td>Euthyroid state Propanolol</td>
<td>Carboanhydrase inhibitors Thiazide-Diuretics Inhaled beta-agonists as needed</td>
<td>Carboanhydrase inhibitors</td>
</tr>
</tbody>
</table>

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Episodic disorders channelopathies
Location of the channels

Na\textsubscript{v}1.4 Na\textsuperscript{+} channels generate AP mutations in the voltage sensors of domains 2 and 3 cause HypoPP-2
Clinically similar to HypoPP-1
Also
HyperPP

Ca\textsubscript{v}1.1 Ca\textsuperscript{2+} channel essential for coupling of excitation-contraction all voltage sensor mutations cause HypoPP-1
4 major types of muscular ion channels

- **Na\(^+\) channels** – membrane excitability
- **Ca\(^{2+}\) channels** – couple membrane excitation to muscle contraction
- **Cl\(^-\) channels** – stabilising the resting membrane potential and help in membrane repolarization after excitation
- **K\(^+\) channels** - membrane repolarization
Cl⁻ channel
Rec. Myotonia congenita
Stiffness + transient weakness

Ca²⁺-channel
hypoPP1 weakness, sensitive to low K⁺

K⁺ sensitivity

Na⁺-channel
hypoPP2 weakness, sensitive to low K⁺

Na⁺-channel
HyperPP weakness, sensitive to increase in K⁺
sometimes stiffness

Muscle channelopathies

Cl⁻ channel
Dominant Myotonia
Pure stiffness

Na⁺ channel
Na⁺ channel myotonia
Pure stiffness

Na⁺ channel
Paramyotonia congenita
Stiffness, weakness, maybe K⁺ sensitive

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After Burge and Hanna 2011
Classical type of electrical excitation

- Δ Membrane potential
- Gating of channels
- Ion fluxes
- Other transport mechanisms
- Other stimuli
Classical type of electrical excitation

- Δ Membrane potential
- Gating of channels
- Ion fluxes
- Other transport mechanisms
- Trigger
  - Shifts in pH, electrolyte concentration, temperature
Free ion concentration and equilibrium potentials for mammalian skeletal muscle

<table>
<thead>
<tr>
<th>Ion</th>
<th>Extracellular concentration (mM)</th>
<th>Intracellular concentration (mM)</th>
<th>$\frac{[\text{Ion}]}{[\text{Ion}]}$</th>
<th>Equilibrium potential (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na$^+$</td>
<td>145</td>
<td>12</td>
<td>12</td>
<td>+67</td>
</tr>
<tr>
<td>K$^+$</td>
<td>4</td>
<td>155</td>
<td>0.026</td>
<td>-98</td>
</tr>
<tr>
<td>Ca$^{2+}$</td>
<td>1.5</td>
<td>100 nM</td>
<td>15,000</td>
<td>+129</td>
</tr>
<tr>
<td>Cl$^-$</td>
<td>123</td>
<td>4.2</td>
<td>29</td>
<td>-90</td>
</tr>
</tbody>
</table>

The skeletal muscles contain the largest single pool of K$^+$ in the body (75% of total). Muscular exercise releases K$^+$ $\rightarrow$ serum K$^+$ $\uparrow$
Inside the cell: high K$^+$ (140 mM), low Na$^+$ (15 mM)
Outside: low K$^+$ (3-5 mM), high Na$^+$ (150 mM)
At rest: high permeability for K$^+$, low for Na$^+$
Concentration maintained by membrane pump
Basis of excitability

- $E_{Na}$
- Membrane potential (mV)
- Na$^+$ conductance (Na$^+$ channels)
- K$^+$ conductance (K$^+$ channels)
- Action potential
- Open channels per $\mu$m$^2$ of membrane

$E_K$
Basis of excitability: resting potential, dependent on $[K^+]$

More complicated than just a deviation from $E_K$ (Nernst potential for $K^+$)

$$E_{Goldman} = \frac{RT}{F} \ln \left\{ \frac{P \times [Na^+]_e + [K^+]_e}{[K^+]_i} \right\}$$

Paradoxical depolarization was initially explained by a block of the Na+/K+ ATPase

$$E_K = \frac{RT}{F} \ln \left\{ \frac{[K^+]_e}{[K^+]_i} \right\}$$

New finding: p.d. at physiological $K^+$
Variability and functionality of P2 in normal muscle?

Healthy fibers ➔ hyperpolarised, if external K+↓

P1 follows Goldman
P2 ~ -60 mV
Electrical membrane bistability (P1, P2) and $[K^+]_o$. 

At P2, most Na$^+$ channels are inactivated: no generation of action potentials

$K = \text{distance from point of contact}$

Reason for bistability and its modification by K?
• Inactivation of Na\(^+\) channels
• = no action potentials \(\Rightarrow\) weakness
• = no membrane excitability
• = no activity in EMG
P1/P2 relation depends on [K$^+$]

**Physiological Na$^+$ leak**

- [K$^+$] = 1 mM
- [K$^+$] = 2.5 mM
- [K$^+$] = 4 mM

**Additional Na$^+$ leak**

- [K$^+$] = 1 mM
- [K$^+$] = 2.5 mM
- [K$^+$] = 4 mM

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**Fig. 1** α-Subunit of the voltage-gated sodium channel of skeletal muscle, Na\textsubscript{v}1.4. The alpha-subunit is composed of four highly homologous domains (DI–DIV) each consisting of six transmembrane segments (S1–S6). When inserted in membrane, the four domains of the protein fold to generate a central pore whereby the S5–S6 loops form the ion-selective pore. The S4 segments contain positively charged residues conferring voltage dependence to the protein. Domains are connected by intracellular loops; one of them, the DIII–DIV linker, contains the inactivation particle of the channel. The sketch gives an overview of locations of known Na\textsubscript{v}1.4 mutations.
Leak current via $\omega$-pore

Activated by hyperpolarisation

Counteracts Kir2.1 current

Depolarizes and destabilizes the resting membrane potential

→ Fraction of P2↑

$\omega$-current is independent from the ion-selective $\alpha$-pore
Depending on the mutation, ω-currents can be induced by hyperpolarisation or by depolarisation, often different reaction to oral K⁺ administration.

Gating pore current very small about 1% of the alpha-pore current that elicits the AP.

ω-current usually Na⁺-current, possibly also H⁺ (external acidification, could explain why attacks preferentially occur during the recovery period following muscle exercise).
In HypoPP, all but one mutation are pointmutations that neutralize positive charged arginine in the S4 Segment of Na\textsubscript{v}1.4 or Ca\textsubscript{v}1.1. Arginine voltage sensor mutations in 90% of HypoPP.
Bistable membrane potentials

Beginning at high K\(^+\) concentrations, a reduction reveals an instability of the resting potential at the limit point, LP1 (closed circles), from which a sudden transition to about -60 mV occurs. Increasing the K\(^+\) concentration from low values takes the muscle fiber to another limit point, LP2 (open circles), where the system jumps back into a state with normal membrane potentials. (red line), In the presence of an omega-pore (blue line), the membrane instability occurs at mild K\(^+\) reduction. Smaller omega-currents, more severe hypokalemia necessary for shift to P2.

Fraction of rat diaphragm muscle fibers with normal membrane potentials after the reduction of \([K^+]_o\) to different values, without (red) and with (blue) amphotericin B, a Na\(^+\) and K\(^+\) ionophore (= mimicking hypoPP)

Probability density functions give the probability of a transition from the normal to the depolarized state for responding fibers at different \([K^+]_o\). LP1 is the mode or the median of the curves. Amphotericin B causes an increment of mode, median, and SD by 1 mM, 1.5 mM, and 1.2 mM.

\(\Rightarrow\) in the presence of a small depolarizing leak current, LP1 is shifted to the right and a paradoxical depolarization is more likely to occur even at normal \([K^+]_o\)
Transverse tubular system (TTS) of an adult muscle fiber.

Electrolyte and water dysequilibrium during paralytic attacks cause a vacuolar myopathy, a proliferation of TTS and SR.

Poor correlation between weakness and vacuolar myopathy.
Hypothesis: development of muscle dystrophy

- Normal: full muscle strength
- Intracellular Na\(^{+}\) accumulation and edema
- Reversible weakness
- Fibrosis and fatty replacement
- Irreversible weakness

Triggers:
- CAI, aldosterone
- Antagonists, K\(^{+}\)

With years:

- HypoPP family

Images:
- T1W
  - 25 y.
  - 52 y.
  - 80 y.
Conclusions

severe mutations (= large leak):
- high intramuscular resting $\text{Na}^+$
  - reversible permanent weakness
  - irreversible weakness, fatty muscle replacement

less ictal $\text{Na}^+$ increase
milder ictal hypokalemia

TX: $\text{K}^+$-sparing, $\text{Na}^+$ extruding diuretics

mild mutations (= small leak):
- lower intramuscular resting $\text{Na}^+$
  - larger ictal $\text{Na}^+$
    - fiber swelling, compartment syndrome
    - vacuolar myopathy

larger ictal hypokalemia
- possibly lethal hypokalemic cardiac arrhythmia

TX: ictal $\text{K}^+$ substitution
The principle of paradoxical depolarization upon serum K⁺-reduction that underlies HypoPP pathogenesis may apply to all tissues equipped with Kᵢᵣ channels (brain, heart, muscle, kidney, leukocytes)
Higher total sodium concentrations can be detected in lesions and, to a lesser extent, in the normal-appearing white matter in patients with multiple sclerosis.
Weakness
phenomenology

• Episodic weakness (generalized, one side, focal)
• Bulbar and respiratory muscles rarely affected
• Commonly in the morning after waking up
• Triggers: stress, cold, fasting (hyperPP), carbohydrate-rich meal (hypoPP), exercise followed by rest
• Tendon reflexes depressed during the attack
• Later onset myopathy (hyperPP, hypoPP)
• Not necessarily flaccid (muscles can be stiff due to influx of Na\(^+\) and water)
Hypokalemic periodic paralysis estimated prevalence of 1 in 100,000
HypoPP may be familial with autosomal dominant inheritance
Clinical penetrance is often incomplete, especially in women
The disorder is three to four times more commonly clinically expressed in men.
hypoPP not confined to man, also in Burmese cats
mutation in the gene that codes for the \( \alpha-1 \) subunit of the dihydropyridine-sensitive calcium channel in skeletal muscle is found in about 70% of patients; this mutation reduces channel availability. An aberrant pore in the voltage sensor allows a persistent inward Na\(^+\) flow, which depolarizes the membrane and makes the fibers inexcitable.

A mutation in the skeletal muscle sodium channel, SCN4A, is responsible for this syndrome in other families. The mutation stabilizes the inactivated state.

Approximately one third of cases represent new mutations; eg phenotype with mutation of ATP1A2-gen (Gen for the Na\(^+\)/K\(^+\)-ATPase in the muscular membrane and in the brain)

or systemic metabolic abnormalities downstream the effects on electrophysiology, e.g. abnormal AMP-activated protein kinase activation in SCN4A-Mutations (AMPK = enzyme that protects the cell from lack of ATP)
What evidence suggests Periodic Paralysis?

Family and own history of weakness episodes, attacks more frequent in males

Normal serum $K^+$ between spells (usually in the lower range)

Sensitivity to serum $K^+$

Muscle cramps/pain

Permanent weakness, progressive with age

Typical triggers, age of onset, serum $K^+$ alterations during spells

**Mutation** is the final proof

HypoPP: spells hours to days, response to low-$Na^+$ & high-$K^+$

HyperPP: short spells, myotonia, response to low-potassium
What are triggers of HypoPP weakness spells?

• **Stress** (*release of adrenaline that causes hypokalemia*)
• **Infections** and **vaccinations** (*release of inflammation factors, could be suppressed by ibuprofen*)
• **Surgery** (stress, pure glucose and NaCl infusions)
• **Cold** environment
• **Hormones** adrenaline, estrogen (contained in birth control pills)
• **Rest** after **strenuous work**
• **Awakening** from sleep
• **Certain food & beverages**
• High glycemic index (GI) **carbs**: pasta, soft drinks (Coke), lemonade, alcohol, some juices, starch, chinese food
• **Sodium salts** (chips) (*hypernatriemia causes diuresis and K⁺ wasting; avoiding NaCl as good as med!*)
• **Cortisol** (inhibits GLUT4-R, (Glucose-Transporter-R.)
• **Certain drugs**
Why are triggers so important?

- Helpful for DX of the phenotype
- Important for management (avoid the triggers)
- Eg misdiagnosis of conversion disorder; stress as a trigger vs carb as a trigger
What can prevent weakness spells?

- Serum K⁺ in the high normal range or slightly above (4.5 to 5.2 mM)

- Low-sodium and low-carb food

- Continuous mild exercise (“keep moving”)

- Warmth

- Adequate physical therapy

- Stress avoidance

- Medication (K⁺, eplerenone, CAI)
Medicines for HypoPP

**Acute:**
Potassium

**Chronic:**
1) Potassium
2) Carbonic Anhydrase Inhibitors (Diamox, Dichlorphenamide)
3) Aldosterone Antagonists (Spironolactone, Inspra)
4) K-sparing Diuretics (Triamterene, Amiloride)
5) Beta-blockers (Propranolol)

If weakness is permanent, consistent and continuous ingestion is required
How does $K^+$ work?

**Beneficial effects of $K^+$**
$K^+$ shifts P2 to P1, increases strength & circulation

**Disadvantages of oral potassium ingestion**
Can cause stomach pain
High serum peaks will cause release of aldosterone resulting in $K^+$ wasting (vicious circle)
$K^+$ competes with other substances for intestinal absorption (e.g., vitamine B12)

**Aim:** Raise serum $K^+$ by reduced excretion!
How do Aldosterone Antagonists work?

Raise serum $K^+$ (by reduced excretion) that shifts P2 fibers to P1, thereby increasing strength & circulation

**Old Substance:**
Spironolactone (major hormonal side effects such as male breast enlargement and tenderness)

**Relatively New Substance:**
Eplerenone/Inspra (minor hormonal side effects)
Important

However, Serum $K^+$ in HypoPP usually is in the lower normal range (3.5 to 4.2 mM) even between spells; it is really difficult to raise it!

In the attack, additional uptake of $K^+$ into the muscle!

Only in case of a kidney insufficiency, additional oral $K^+$ ingestion or combination with $K^+$-increasing drugs may cause dangerous hyperkalemia (check serum $K^+$ frequently!)
How do potassium-sparing diuretics work?

Raise serum $K^+$ (by reduced excretion) that shifts P2 fibers to P1, thereby increasing strength & circulation

Triamterene (Dyrenium®, Dytac® 50 mg/100 mg cps.)

Amiloride (Midamor® 5 mg tbl.)

I’m interested to learn more from users!
How do Carbonic Anhydrase Inhibitors work?

Diamox shifts P2 fibers to P1 (via activation of K⁺ channels), thereby increasing strength & circulation!

As Carbonic Anhydrase Inhibitor (CAI), Dichlorphenamidine is more potent and permeates the membrane more easily than Diamox does.
Side effects of Carbonic Anhydrase Inhibitors

Nausea and dizziness at the beginning (take it with food and start with low dose and increase gradually)

Paresthesias

Strange taste (do not take carbonated drinks)

Kidney Stones can be avoided by K⁺-citrate!
How do Beta Blockers work?

Beta1-Blockers indirectly inhibit Aldosterone
*examples: Metoprolol, Bisoprolol, Atenolol*

Beta2-Blockers assist in avoiding stress-triggered weakness spells

*examples for Nonselective-Beta Blockers: Propranolol, Timolol, Bupranolol*

Adverse effects: reduce heart rate and blood pressure

Beta-Blockers are widely accepted for Thyrotoxic HypoPP but so far not for Familial HypoPP
My belief:

If long-term medication is required, combine 2 meds of different groups at low-dose, e.g. Dichlorphenamid and an aldosterone antagonist, and try to keep additional K⁺ as low as possible.

The low doses of each med will keep adverse effects minimal.
Modification of HypoPP by sexual hormones

Majority of females report premenstrual symptoms (uterus cramps, muscle weakness)

Some report worsening with birth control pills (usually contain both estrogen + progesterone)

Majority report improvement during pregnancy (increase in progesterone), those might benefit from a progesterone-only pill
What drugs worsen HypoPP?

• **Drugs** reducing neuromuscular transmission, i.e. those contraindicated when *myasthenic*: Muscle Relaxants, Antibiotics like aminoglycosides, macrolides, fluoroquinolones

• **Drugs** causing **hypokalemia** (& hypophosphatemia): Albuterol (and other beta-2 sympathicomimetics against asthma), Penicillin, Cortisol, most diuretics, laxatives, Liquorice, Bactrim

• **Drugs** causing muscle ischemia (Epinephrine)

• **Myotoxic substances** such as Statins (recommended only to HypoPP with high infarction risk)
What does determine the individual prognosis?

1) Type of mutation

The 2 extreme ends of the HypoPP spectrum:

severe hypokalemia during spell may cause arrhythmia but no progressive weakness

mild or no hypokalemia but progressive weakness

2) Genetic background (family)

3) Environmental factors, e.g. life-long strong physical work favours development of permanent weakness
hyperPP
pathophysiology

• hyperPP, the Na\(^+\) channel closes too slowly, Na\(^+\) ions continue to leak into the muscle cell
• ➔ oversensitivity and stiffness in the muscle (myotonia)
• If the channel remains open, the muscle will become desensitized and paralyzed
• During the episode of muscle weakness or paralysis, K\(^+\) ions are released from the muscle
• ➔ \([K^+]_o \uparrow\)
Different effects of HypoPP and HyperPP mutations explain contrary clinical features

Hypokalemia leads to transient hyperpolarization followed by sustained depolarization (weak)

Hyperkalemia induces slight depolarization which opens channels that can’t inactivate
Vicious circle in hyperPP

- $K^+_{extracellular} \uparrow$
- depolarization
- $Na^+_{channel\ opening}$
- $K^+_{efflux}$
- myotonia
- paralysis

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### Features of hyperkalemic PP (hyperPP)

<table>
<thead>
<tr>
<th>Transmission:</th>
<th>autosomal dominantly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence:</td>
<td>1:200,000</td>
</tr>
<tr>
<td>Onset of disease:</td>
<td>childhood or puberty</td>
</tr>
</tbody>
</table>
| Clinical features: | attacks of generalized muscle weakness  
| | ictal increase in serum potassium  
| | EMG myotonia  
| | progressive myopathy |
| Frequency of attacks: | daily for minutes to hours |
| Provocative factors: | K⁺ rich food, fasting,  
| | cooling, mental stress, pregnancy  
| | resting periods after exercise |

red: new; blue: contrary to hypoPP
HyperPP

TX
no ω-pore, but deficient Na⁺channel inactivation

• Acute attacks often do not require treatment, as they are brief.
• Some patients can abort attacks with sugar or mild exercise
• Stimulation of the Na⁺-K⁺-pump, increasing K⁺ transport into cells (continuous mild exercise, carbohydrate ingestion, inhaled beta adrenergic agonists (eg, one to two puffs of 0.1 mg albuterol))
• intravenous calcium
• Thiazid-diuretics, CAI

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View from Ulm University of Ulm Munster and the Alpes