Muscular Channelopathies
Periodic Paralysis

Department of Neurology
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And
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Frank Weber

Frank Lehmann-Horn, Senior Research Professor

Weber Dublin 2018
Sein Optimismus wird uns fehlen
Wir trauern um
Prof. Dr. Dr. h. c.

Frank Lehmann-Horn
* 22. 6. 1948  † 8. 5. 2018

Christa
Klaus und Saskia
mit Verena und Vivien
Jochen und Annelise
mit Lily und Sophie
Thomas und Rebecca
im Namen aller Angehörigen

Der Trauergottesdienst findet
am Dienstag, dem 15. Mai 2018, um 13.00 Uhr
in der Petruskirche Neu-Ulm statt.
# 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 yrs</td>
<td>&lt; 10 yrs</td>
<td>&lt; 20 yrs</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>Nonpenetration common (women)</td>
<td>High</td>
<td>Nonpenetration and incomplete penetrance common</td>
<td></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 intrafamilial 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 muscular ion channels

\[ \text{Na}_v1.4 \text{ Na}^+\text{-channels generate AP} \]

Mutations in the voltage sensors of domains 2 and 3 cause HypoPP-2

Clinically similar to HypoPP-1

Also

HyperPP

PMC

PAM

CMS

\[ \text{Ca}_v1.1 \text{ Ca}^{2+} \text{ channel essential for coupling of excitation-contraction} \]

all voltage sensor mutations

cause HypoPP-1

Kir channel

Kir conductance $\downarrow$ $\rightarrow$

paradoxical depolarization

Kullmann DM. 2010.

Annu. Rev. Neurosci. 33:151–72
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
**Muscle channelopathies**

- **Cl⁻ channel**
  - Dominant Myotonia
  - Pure stiffness

- **Na⁺ channel**
  - Myotonia
  - Pure stiffness

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

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

- **K⁺ sensitivity**
  - HypoPP2 weakness, sensitive to low K⁺, very rare stiffness

- **K⁺-channel**
  - hyperPP weakness, sensitive to increase in K⁺, sometimes stiffness

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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

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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>[Ion]_o/[Ion]_i</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>Ca²⁺</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⁺ → serum K⁺ ↑ Skeletal muscle regulates extracellular K⁺ by taking up or releasing the ion.
Some definitions

- HypoPP = hypoKPP, $[K^+]_o < 3.5$ mmol/L
- HyperPP = hyperKPP, $[K^+]_o > 5$ mmol/L
- Important: In my experience - although against the definition - in both disorders, serum $K^+$ in the attack is not necessarily outside the normal range!
- Personal proposal:
  - hypoPP = episodes triggered by shift of $K^+$ $\downarrow$ AND improvement by shift of $K^+$ $\uparrow$
  - hyperPP = episodes triggered by shift of $K^+$ $\uparrow$ AND improvement by shift of $K^+$ $\downarrow$
- Cave: during the episode
- HypoPP: uptake of $K^+$ by muscle
- HyperPP: additional release of $K^+$ by muscle
- $\Rightarrow$ both can result in severe dyskalemia
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

Diagram showing the relationship between membrane potential and conductance of sodium (Na⁺) and potassium (K⁺) channels, with an action potential indicated. The axes represent membrane potential (mV) and open channels per µm² of membrane, respectively.
Basis of excitability: resting potential, dependent on $[K^+]$

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

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

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

Paradoxical depolarization was initially explained by a block of the Na$^+$-K$^+$-ATPase

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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\(^+\)?
**Figure 1.** R222W affects resting and action potentials in muscle fibers. The density of muscle fibers at various resting membrane potentials shows peaks at $P_1$ (hyperpolarized) and $P_2$ (depolarized) for control and R222W (A). $P_1$ peaks are $-80.9 \pm 0.1$ mV (control) and $-74.5 \pm 0.4$ mV (R222W), with $P_2$ peaks at $-60.2 \pm 0.4$ mV (control) and $-58.4 \pm 0.4$ mV (R222W). Action potentials in R222W ($n = 10$) fibers have a maximum amplitude of $-8 \pm 5$ mV, significantly ($P \leq 0.05$) less than that for control fibers ($n = 6$) at $+11 \pm 8$ mV (B).

**Na$_\nu$1.4 DI-S4 periodic paralysis mutation R222W enhances**
• 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 \(\alpha\)-Subunit of the voltage-gated sodium channel of skeletal muscle, \(\text{Na}_v\). The \(\alpha\)-subunit is composed of four highly homologous domains (D1–D4) 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 \(\text{Na}_v\) mutations.
Ca\textsubscript{v}1.1 mutations

- **HypoPP type 1:** R528H/G/C, R897S/T, R900S, R1239H/G, R1242G
- **Recessive mutations in congenital myopathy:** E100K, F275L, S397Pfs*3, L791Cfs*37, Q1265Hfs*57, Q1485*, L1656Rfs*67
- **Dominant mutations in congenital myopathy:** P742S/Q, L1367V
- **NormoPP linked mutation** R1242G (DIV/S4 R3)
HypoPP1 mutation generate an **inward gating pore current** at negative voltages **through a pathway** located within the voltage-sensing domain and **distinct from the main Ca\(^{2+}\) conducting pore**.
Leak current via ω-pore

Activated by hyperpolarisation

Counteracts Kir2.1 current

Depolarizes and destabilizes the resting membrane potential

⇒ Fraction of P2 ↑

ω-current (gating pore current) is independent from the ion-selective α-pore

- In general, ω-current and amplitude depend on the number of charges in S4
- the position of the mutated S4 charge and countercharges
- nature of the replacing amino acid.
Depending on the mutation, $\omega$-currents can be induced by hyperpolarisation or by depolarisation, often different reaction to oral $K^+$ administration.

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

$\omega$-current usually Na$^+$-current, possibly also H$^+$ (eg in R1239H mutations. External acidification could explain why attacks preferentially occur during the recovery period following muscle exercise.)
In normal external K⁺ and neutral external pH, the outward current through Kir channels dominates over inward leak currents. The resting potential is close to the K⁺ equilibrium.

Fall in external K⁺, possibly caused by over-activity of the Na⁺-K⁺ pump → decrease in the Kir conductance aggravated by external acidosis that further inhibits Kir channels → resting potential less negative value → outward currents through Kv channels + Kir channels balance the inward H⁺ or Na⁺ depolarizing currents. This depolarized resting potential promotes inactivation of Naᵥ, inexcitability and muscle paralysis.
• In HypoPP, all but one mutation are point mutations that neutralize positive charged arginine in the S4 Segment of Na$_v$1.4 or Ca$_v$1.1
• Arginine voltage sensor mutations in 90% of HypoPP
• Mutations of the outermost gating charges (R1 and R2)
  $\rightarrow$ hypoPP
  $\rightarrow$ creating a pathogenic gating pore in the voltage sensor
• Mutations of the third gating charge (R3) $\rightarrow$ normoPP
• $\rightarrow$ cation leak in both activated and inactivated states
• Mutations create an aequous path through the membrane.

$\Rightarrow$ It is the leak, that matters, and not, whether the leak is in the Ca$^{2+}$ or in the Na$^+$-channel!
Bistable membrane potentials

**Bistability** also occurs in neurons

**physiologically** in respiratory center and motoneurons (AP bursts from reduced plateau potential)

**pathologically** in neurons not able to repolarize (neurodegeneration)

• 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.
Large P2 fraction + weakness if

1. Inward sodium leak (ionophores)
2. Severe hyperkalemia (kidney insuff.)
3. Severe hypokalemia (Bartter)
4. Mild hyperkalemia + leak (Na⁺-Ch-Myotonia)
5. Mild hypokalemia + leak (HypoPP)
6. Reduced outward current (ATS) (ATS Kir2.1, outward K⁺ currents through mutant Kir is always smaller than inward leak current → balance between outward and inward currents can only be reached if resting membrane potential is shifted to depolarized membrane potential where outward K⁺ current is mediated by Kv, same net effect as inward Na⁺ leak)
Large P2 fraction + weakness

- Kir reduction has the same effect as a leak

Computer model
Positive feedback cycle for development of hypokalemia via paradoxical depolarization of skeletal muscle membrane potential. Exercise and adrenal steroids stimulate Na⁺-K⁺-Pump. Insulin, catecholamines, thyroid hormones, caffeine, etc can both stimulate Na⁺-K⁺-ATPase and inhibit Kir.
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:

- 25 y.
- 52 y.
- 80 y.

HypoPP family

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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 $\text{Na}^+$ $\uparrow$
  - 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). MS: Na⁺ channel upregulation, redistribution, mitochondrial dysfunction
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, Na\(^+\) intake
• 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)
Features of hypoPP

Prevalence
1 in 100,000 (1 in 200,000 NL, 2018)

Transmission
familial, autosomal dominantly
Clinical penetrance often incomplete, especially in women, in men 3x to 4x more commonly clinically expressed

Natural animal model
Burmese cats

Cause
mutation in the gene that codes for the α-1 subunit of Ca\textsubscript{v}1.1 (CACNA1S) or of Na\textsubscript{v}1.4 (SCN4A)

Approximately one third of cases represent new mutations; eg phenotype with mutation of ATP1A2-gen (Gen for the Na\textsuperscript{+}-K\textsuperscript{+}-ATPase in the muscular membrane and in the brain) ➔ also in this case a leak in the membrane, but different syndrome (PP+)

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)
### Table 1
Demographic characteristics and minimum point prevalence rates of the skeletal muscle channelopathies in the Netherlands.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Patients N (pedigrees)</th>
<th>Mean age, years (SD)*</th>
<th>Female (%)</th>
<th>Prevalence rate × 10⁻⁵ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMC</td>
<td>405 (234)</td>
<td>44 (±19)</td>
<td>53</td>
<td>2.38 (2.16–2.63)</td>
</tr>
<tr>
<td>NDM</td>
<td>288 (188)</td>
<td>43 (±20)</td>
<td>52</td>
<td>1.70 (1.55–1.95)</td>
</tr>
<tr>
<td>MC</td>
<td>128 (108)</td>
<td>42 (±19)</td>
<td>47</td>
<td>0.75 (0.63–0.90)</td>
</tr>
<tr>
<td>PMC/SCM</td>
<td>160 (80)</td>
<td>45 (±20)</td>
<td>56</td>
<td>0.94 (0.81–1.10)</td>
</tr>
<tr>
<td>PP</td>
<td>117 (46)</td>
<td>47 (±21)</td>
<td>54</td>
<td>0.69 (0.57–0.83)</td>
</tr>
<tr>
<td>HypoPP</td>
<td>90 (35)</td>
<td>49 (±21)</td>
<td>52</td>
<td>0.53 (0.43–0.65)</td>
</tr>
<tr>
<td>HyperPP</td>
<td>10 (7)</td>
<td>35 (±15)</td>
<td>63</td>
<td>0.06 (0.03–0.12)</td>
</tr>
<tr>
<td>ATS</td>
<td>17 (6)</td>
<td>40 (±20)</td>
<td>59</td>
<td>0.10 (0.06–0.16)</td>
</tr>
</tbody>
</table>

Numbers represented the whole disease group of SMC, the two disease categories (NDM and PP) within the SMC, and subtypes within the disease categories (MC, PMC/SCM, HypoPP, HyperPP and ATS).

Abbreviations: SD = standard deviation; CI = confidence interval; SCM = skeletal muscle channelopathies; PP = primary periodic paralyses; NDM = non-dystrophic myotonia; MC = myotonia congenita; SCM = sodium channel myotonia; PMC = paramyotonia congenita; HypoPP = hypokalemic periodic paralysis, HyperPP = hyperkalemic periodic paralysis; ATS = Andersen–Tawil syndrome.

* At time of the prevalence day.
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
Triggers of hypoPP weakness spells

- **Stress** *(release of adrenaline causes hypokalemia via Na\(^+\)-K\(^+\)-pump↑)*
- **Infections** and **vaccinations** (release of inflammation factors, can 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** (exercise transitory K\(^+\) release, post exercise hypokalemia due to overactivity of the Na\(^+\)K\(^+\)-pump, external acidification)
- **Awakening** from sleep
- Certain **food & beverages**
- High glycemic index (GI) **carbs**: pasta, soft drinks (Coke), lemonade, alcohol, some juices, starch, chinese food *(insulin dual action → K\(^+\) uptake↑ via Na\(^+\)-K\(^+\)-pump↑ = hypokalemia + inhibitory effect on Kir currents, thus inhibiting K\(^+\) release from muscle)*
- **Sodium salts** (chips) (hypernatriemia causes diuresis and K\(^+\) wasting; avoiding NaCl as good as med!)
- **Cortisol** (inhibits the Glucose-Transporter-R. GLUT4-R)
- Certain **drugs**
Triggers of hypoPP weakness spells

- Some triggers trigger the activity of the Na⁺-K⁺-pump in the muscle.
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”, release of $K^+$ from the muscle fiber with activation)

- Warmth

- Adequate physical therapy

- Stress avoidance

- Medication ($K^+$, eplerenone, CAI)
Effect of muscular exercise on K⁺

PLASMA POTASSIUM AND HIGH INTENSITY EXERCISE

Fig. 1. Arterial and femoral–venous plasma potassium concentration before and after 1 min exhausting exercise (series 1; means ± s.e.m., n = 12).

Journal of Physiology (1990), 421, pp. 105–122

12 healthy volunteers
Drugs against HypoPP

• Acute
  • Potassium

• Chronic
  • Potassium
  • Carbonic Anhydrase Inhibitors (Diamox, Dichlorphenamide)
  • Aldosterone Antagonists (Spironolactone, Eplerenone)
  • $K^+$-sparing Diuretics (Triamterene, Amiloride)
  • 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 $\rightarrow$ increases strength and 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?

Serum K\(^+\) ↑ (by reduced excretion) that shifts P2 fibers to P1 → increases strength and circulation

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

Relatively new Substance
Eplerenone/Inspra (minor hormonal side effects)
Eplerenone

• Eplerenone increases in vitro the proportion of polarized muscle fibers

Scharrer 2013

blue normal
Red Ionophore (Amphotericin B, artificial leak)
Green Amphotericin B + Eplerenone
Important $K^+$ issues

• 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?

- Serum $K^+$ \(\uparrow\) (by reduced excretion) that shifts P2 fibers to P1 $\rightarrow$ increases strength and circulation

- Triamterene (Dyrenium\textsuperscript{®}, Dytac\textsuperscript{®} 50 mg/100 mg cps.)

- Amiloride (Midamor\textsuperscript{®} 5 mg tbl.)
How do Carbonic Anhydrase Inhibitors (CAI) work?

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

• As CAI, Dichlorphenamide is more potent and permeates the membrane more easily than Diamox does.

• Acetazolamid beneficial in about 50% of patients with $Ca_{v}1.1$ mutations, often ineffective in patients with $Na_{v}1.4$ mutations.
CAI side effects

• Nausea and dizziness at the beginning
  – take them with food
  – start with low dose
  – 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
Significance

Voltage-gated ion channels contain domains that have discrete functionalities. The central pore domain allows current flow and provides ion selectivity, whereas peripherally located voltage-sensing domains (VSDs) are needed for voltage-dependent gating. Certain mutations trigger a leak current through VSDs, known as gating pore current. Hypokalemic periodic paralysis (HypoPP) type 2 is caused by mutations in the skeletal muscle voltage-gated sodium channel Na\textsubscript{v}1.4 that neutralize positive charges in S4 voltage-sensing segments of VSDs. We show that Hm-3 toxin from the crab spider *Heriaeus melloteei* inhibits gating pore currents through such mutant channels. We propose that Hm-3 and similar toxins may constitute useful hits in developing gating pore current inhibitors and HypoPP therapy.
My belief

• If long-term medication is required:
  • combine 2 meds of different groups at low dose, e.g. Dichlorphenamidine and an aldosterone antagonist
  • 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 (progesterone ↑) → benefit from a progesterone-only pill possible
Which drugs do 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?

• Type of mutation
  
  • The two extreme ends of the HypoPP spectrum:
    
    • severe hypokalemia during spell may cause arrhythmia but no progressive weakness
    
    • mild or no hypokalemia but progressive weakness
  
• Genetic background (family)

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

- hyperPP: 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 paralysed
- 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

Glucose

HypoPP

HyperPP

K⁺-rich food

aberrant pore

Low K⁺

external

High K⁺

central pore

Glucose

K⁺-rich food

aberrant pore

Low K⁺

external

High K⁺

central pore

Glucose

K⁺-rich food

aberrant pore

Low K⁺

external

High K⁺

central pore

mV

nA/mm²

150 mM NaMS

Jurkat-Rott et al. PNAS 2009

Weber Dublin 2018
Vicious circle in hyperPP

$K^+_{\text{extracellular}} \uparrow \quad \rightarrow \quad \text{depolarization} \quad \rightarrow \quad \text{Na}^+ \text{ channel opening} \quad \rightarrow \quad \text{paralysis}$

$K^+ \text{ efflux} \quad \rightarrow \quad \text{myotonia} \quad \rightarrow \quad \text{paralysis}$
<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission</td>
<td>autosomal dominantly</td>
</tr>
<tr>
<td>Prevalence</td>
<td>1:200,000 (0.12:200,000 NL, 2018)</td>
</tr>
<tr>
<td>Onset of disease</td>
<td>childhood or puberty</td>
</tr>
<tr>
<td>Clinical features</td>
<td>attacks of generalized muscle weakness</td>
</tr>
<tr>
<td></td>
<td>ictal increase in serum potassium</td>
</tr>
<tr>
<td></td>
<td>EMG myotonia</td>
</tr>
<tr>
<td></td>
<td>progressive myopathy</td>
</tr>
<tr>
<td>Frequency of attacks</td>
<td>daily for minutes to hours</td>
</tr>
<tr>
<td>Triggers</td>
<td>K⁺ rich food, fasting, cooling, mental stress, pregnancy, rest after exercise</td>
</tr>
</tbody>
</table>
TX of HyperPP

- 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
View from Ulm University of Ulm Munster and the Alpes