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New Research and Drug Therapie
PP Hypo Survey
Thymus Hyperplasia

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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
Variability and functionality of P2 in normal muscle?

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?
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
Hypothesis: development of muscle dystrophy

- Normal: full muscle strength
- Intracellular Na\(^+\) accumulation and edema: reversible weakness
- With years: fibrosis and fatty replacement; irreversible weakness

Triggers: CAI, aldosterone Antagonists, K\(^+\)
Conclusions and hypothesis

P1
resting state

P2
non-activatable,
reversible state

K+, K\textsubscript{ATP} opener, diuretics

low K, omega pore increases influence of low K

irreversible degeneration

activated state

edema

vacuolar myopathy
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

Jurkat-Rott et al. PNAS 2009
Conclusions

severe mutations: high intramuscular resting Na+ (= large leak) >> reversible permanent weakness >>> irreversible weakness, fatty muscle replacement

less ictal Na+ increase
milder ictal hypokalemia

therapy: K+-sparing, Na+ extruding diuretics

mild mutations: lower intramuscular resting Na+ (= small leak)
greater ictal Na+ increase
>> fiber swelling, compartment syndrome
>>>> vacuolar myopathy

greater ictal hypokalemia
>> lethal hypokalemic cardiac arrhythmia

therapy: ictal K+ substitution
Drugs which stabilize cells in the P1 state

Carbonic anhydrase inhibitors (CAI)
- Acetazolamide
- Dichlorphenamide

Aldosterone antagonists
- Spironolactone
- Eplerenone

Progesterone?
Corticosteroids?

($K_{ATP}$ channel openers)
What evidence suggests Periodic Paralysis

Family and own history of weakness episodes

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
Less important features of PP

Later age of onset is no exclusion criterion

Provocative tests are often negative and dangerous

Muscle biopsy just shows unspecific alterations; only required if genetics is indecisive or if unusual features point to a process to be excluded (permanent pain, very high CK)
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**

**Certain food & beverages**

- High glycemic index (GI) **carbs**: pasta, soft drinks (Coke), lemonade, alcohol, some juices, starch (Pringles)

**Sodium salts** *(chips)* *(hypernatriemia causes diuresis and K wasting; avoiding NaCl as good as med!)*

**Cortisol** *(inhibits GLUT4-R, .......)*

**Certain drugs**
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 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
Medicines for HypoPP

**Acute:**
Potassium

**Chronic:**
1) Potassium
2) Carbonic Anhydrase Inhibitors (Diamox, Daranide)
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
1) 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., vitamin B12)

Aim: Raise serum K by reduced excretion!
2) 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!

Only a kidney insufficiency, additional oral K ingestion or combination with K-increasing drugs may cause dangerous hyperkalemia
(check blood K frequently !)
3) 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!
Amiloride
- blocks the epithelial sodium channel ENaC in the distal nephron
- might develop an acidosis
- inhibits cyclic GMP-gated cation channels in the inner ear
- blocks Na+/H+ exchanger type 1 in the heart
- blocks ASIC (acid sensing ion channels) involved in nociceptors

Triamterene
- blocks ENaC
4) How do Carbonic Anhydrase Inhibitors work?

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

Unknown if Daranide has the same effect!

As Carbonic Anhydrase Inhibitor (CAI), Daranide is more potent and permeates the membrane more easily than Diamox does.
What are the effects of CA-inhibitors (CAI)?

**In serum:** reduce $K^+$ & $HCO_3^-$, increase $Cl^-$

**In muscle:** reduce $lac^-$ (via extrac. CA-IV/XIV inhibition) reduce $Na^+$ (via intracellular CA-II inhibition)! increase force by an SR-CaATPase block!!
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!
5) 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. Daranide and an aldosterone antagonist, and try to keep additional K as low as possible.

The low doses of each med (e.g. Daranide 50 mg and Spironolactone 100 mg) 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 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
Hypokalemia can also cause pain & arrhythmia

In HypoPP, exhausting physical exertion causes hypokalemia resulting in muscle cramps and muscle ischemia which may destroy muscle fibers
Anectodal success stories

Minocycline (tetracycline-like, used in an ALS trial)
Metazolamide, another CAI (add-on)
Topamax, another CAI (add-on)
4-aminopyrididine (FampyraR) or 3,4-DAP, K channel blockers
Diet Coke (is it the phosphate?)

Best drug would be an inhibitor of the HypoPP leak:
Diseases similar to HypoPP

HyperPP

Andersen-Tawil syndrome

Episodic Ataxia Type 1,2 (rapid onset and recovery)

Bartter Syndromes

Mitochondrial Diseases

Acquired Channelopathies (autoimmune disease)

Congenital Myasthenic Syndromes
Thymus hyperplasia

- No sound scientific evidence for a causal role in periodic paralysis
- Current policy:
  - We favor thymectomy in case of PP + thymus hyperplasia
Rational for thymectomy in cases of PP + thymus hyperplasia

• Thymus hyperplasia in the adult is certainly abnormal
• Thymus hyperplasia is often associated with antibodies against the neuromuscular junction (eg. MG)
• In case of MG, failure to detect AB against the neuromuscular junction is not unusual (AB-negative MG)
• AB against the neuromuscular junction certainly aggravate PP
• Weakness in the presence of thymus hyperplasia is often improved by cholinesterase inhibitors
Hypokalemic Periodic Paralysis Induced by Thymic Hyperplasia and Relieved by Thymectomy

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**Importance** Hypokalemic periodic paralysis is a muscle channelopathy based on mutations or predisposing variants or secondary to potassium wasting. In contrast to myasthenia gravis, an association with thymic hyperplasia has not yet been reported, to our knowledge.

**Observations** We report a male patient in his mid-20s with progressive episodes of flaccid muscle weakness, associated low serum potassium levels, and a pathologic decrement in the long exercise test. Because the familial inheritance in the family was initially unknown, thorough diagnostic tests were performed including contrast-enhanced computed tomography scan, which displayed a mass in the anterior mediastinum. The test results for autoantibodies against myasthenia gravis (acetylcholine receptor, muscle-specific tyrosine kinase, and low-density lipoprotein receptor-related protein 4) and other end plate channelopathies were negative, and test results for hypokalemic-inducing hormones (thyroid, corticotropin, and cortisol) were negative. Surgery identified a thymus of $13 \times 8 \times 3$ cm$^3$. Histologic analysis was consistent with thymic hyperplasia of the follicular subtype and immunohistologic analysis showed cytokeratin 5/6 in hyperplastic epithelial cells. A 2-year follow-up revealed the postoperative absence of weakness episodes. As in 30% of familial cases, molecular genetics testing failed to identify a mutation in periodic paralysis genes.

**Conclusions and Relevance** Thymic hyperplasia can clinically manifest susceptibility to hypokalemic periodic paralysis. For patients with late onset or increasing weakness episodes, we recommend imaging to assess for thymic enlargement and thymectomy at thymic hyperplasia.

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