In 1865, Claude Bernard wrote that ‘the constancy of the internal milieu is the essential condition to a free and independent life’ [1]. It would be hard to find a more illustrative paradigm for that statement than for the case of hyperkalaemic periodic paralysis (HyperPP) reported by Grgic et al. in this issue [2]. A 14-year-old male was admitted for a sudden ascending paralysis involving the four limbs that appeared shortly after exercise. The symptoms were associated with a severe hyperkalaemia (6.3 mmol/L). Remarkably, both the muscle strength and the K⁺ level normalized spontaneously within 2 h. Since the patient had presented similar episodes since childhood, a clinical diagnosis of HyperPP was made, later confirmed by provocation with exercise and oral K⁺ intake. Genetic analysis detected a known mutation (T704M) in the SCN4A gene that encodes the α subunit of the Nav1.4 voltage-gated sodium channel. The mutation was not detected in the biological parents of the proband. This case is relevant for K⁺ homeostasis, Na⁺ channelopathies and genotype–phenotype correlations.

Potassium homeostasis

Potassium is the most abundant cation in the human body, with total body stores amounting to 50 mmol/kg in adults. Less than 2% of K⁺ is located extracellularly, and kalaemia is maintained in the narrow range of 3.5–5.0 mmol/L. The compartmentalization of K⁺ inside cells is critical for maintaining cell volume, DNA and protein synthesis, and regulating intracellular pH, enzymatic activities and cell growth. Normal individuals ingesting 80–100 mmol of K⁺ daily remain in balance by virtue of short-term transcellular K⁺ shifts regulated by insulin, aldosterone and β-adrenergic catecholamines (β2 receptors), which increase the cellular K⁺ uptake by stimulating the sodium pump (Na⁺/K⁺-ATPase), and the excretion of 90% of the ingested K⁺ in the urine and the remaining in stool. Since the resting membrane potential primarily depends on the steep transmembrane K⁺ gradient, variations in kalaemia influence the excitability of neuromuscular tissues including the heart and the skeletal muscles [3].

Hyperkalaemia and K⁺ redistribution

Hyperkalaemia is a relatively common and potentially life-threatening condition. If we exclude pseudohyperkalaemia, in which K⁺ exits cells during or after blood sampling, three main mechanisms lead to hyperkalaemia: (i) excess intake; (ii) impaired renal excretion and (iii) redistribution (or transcellular shift) of K⁺ between intracellular and extracellular fluid compartments, too fast to be corrected by renal excretion. Conditions that are associated with variations of the transmembrane K⁺ ratio include severe muscle activity; tissue injury; inorganic metabolic acidosis; increased extracellular osmolality; drugs interfering with insulin, catecholamines or aldosterone; the use of succinylcholine, a myorelaxant that depolarizes the cell membrane; and digitalis intoxication, which inhibits the Na⁺/K⁺-ATPase [4]. HyperPP is another example of the transcellular shift of K⁺ out of the cells, due to mutations in specific voltage-gated sodium channels (Na⁺,Chs) in skeletal muscle cells.

The periodic paralyses, paradigm for muscle channelopathies

The periodic paralyses are rare and dominantly inherited disorders characterized by neuromuscular symptoms (paralysis and myotonia) associated with marked and transitory variations of K⁺ levels in the plasma [5,6] (Table 1). Symptoms usually appear during the first or second decade of life and can be life-threatening if heart or respiratory muscles are involved. The paralysis corresponds to muscular flaccidity (paraplegia or tetraplegia) with reversible hypox/inexcitability of the cells. Myotonia is defined by a delayed relaxation of tensed muscles following a powerful contraction, due to sarcotoxic hyperexcitability [7]. Except for very rare normokalaemic cases [8], periodic paralyses are usually classified by the changes in kalaemia during the crisis: hypokalaemic periodic paralysis (HypoPP) and hyperkalaemic periodic paralysis (HyperPP). These two entities show distinct clinical features. Paralysis expression is constant, whereas myotonia is found only in HyperPP. In general, HyperPP attacks occur in the morning and resolve shortly; whereas HypoPP starts during night, with symptoms lasting up to one day. Triggering factors also differ: K⁺ can provoke HyperPP attacks, whereas carbohydrate-rich or Na⁺-rich meals trigger HypoPP. Cold, emotions, fasting or rest after exercise may also trigger HyperPP crisis. The typical history and transient course of the attacks often suggest the diagnosis, which can be confirmed by
mutation analysis (see below). Provocative tests (K⁺ intake or exercise) are useful in some cases but should be performed with caution. The first treatment for both types of PP is to avoid triggering factors and to normalize plasma K⁺ levels. Carboxy anhydrase inhibitors and diuretics are used to prevent the attacks [5,6].

HyperPP is caused by mutations in the SCN4A gene that encodes the α subunit of the Na₉,Ch Na,1.4 in skeletal muscles [9–11]. Na₉,Chs are pore-forming membrane proteins mediating Na⁺ influx involved in the initiation and transmission of action potentials in excitable tissues such as muscles, heart and nerves [12]. These channels are gated by changes in the membrane potential, switching between the closed, activated and inactivated states according to membrane potential variations (Figure 1A). The activation of Na₉,Chs by membrane depolarization causes Na⁺ influx responsible for the sudden membrane depolarization in the initial phase of the action potential. In response, there is a compensatory outward K⁺ current that perpetuates the process along the membrane. The fast inactivation (within milliseconds) of Na₉,Chs is essential for membrane repolarization [12].

Like all members of the Na₉,Ch family, Na,1.4 is made up of a principal pore-forming α subunit, associated with an accessory β subunit. The α subunit consists of four domains, each comprising six transmembrane segments which form the ion-selective pore and confer the voltage dependence of the protein, whereas the intracellular loop between the domains III and IV is involved in the inactivation process (Figure 1B). SCN4A was an early candidate gene for PP, since in vitro studies demonstrated an abnormal Na⁺ conductance in the muscle cell membrane [13]. Linkage analysis [9] and demonstration of missense mutations [10,11] confirmed that SCN4A was responsible for HyperPP. Since then, eight missense mutations of SCN4A have been identified in HyperPP (Figure 1B). The T704M mutation described by Grđić et al. [2] was first reported in 1991 [10].

Reminiscent of the case discussed here, the mutation cosegregated with HyperPP in two families, but appeared as de novo in the third one [10]. The T704M mutation is detected in half the families with HyperPP, whereas the M1592V mutation accounts for one-third of cases [5,12]. Of interest, phenotype variability due to the T704M mutation has been documented in a family with paralysis periodica paramyotonia [14].

**From mutations to disease**

Most of the SCN4A mutations causing HyperPP are located in the inner part of transmembrane segments or in the intracellular loops (Figure 1B), where they affect the fast inactivation of the channel [15–17]. As compared to wild-type channels, mutant channels show incomplete inactivation resulting in an increased level of persistent Na⁺ current (gain of function) that causes a sustained membrane depolarization [18]. In turn, the sustained depolarization will favour K⁺ release from the cells, causing hyperkalaemia, and inactivate the majority of Na₉,Chs, causing electrical inexcitability of skeletal muscles [6,12].

Mutations in SCN4A are not only detected in HyperPP, but also in a minority of patients with HypoPP (HypoPP type 2) and normokalaemic PP, in paramyotonia congenita, potassium-aggravated myotonia and congenital myasthenia [5,19]. Such diversity raises the issue of genotype–phenotype correlations. At variance with the gain of function mutations of SCN4A causing HyperPP, the majority of mutations associated with HypoPP are located in the voltage-sensing transmembrane S4 segment of the domain II of Na,1.4 (Figure 1B), resulting in a stabilization of the closed state of the channel (loss of function) [20]. However, recent studies demonstrated that HypoPP mutations of arginine residues within the domain II create a cation leakage that is not caused by a defect of the

### Table 1. Main features of the periodic paralyses

<table>
<thead>
<tr>
<th></th>
<th>Familial hyperkalaemic periodic paralysis (HyperPP)</th>
<th>Familial hypokalaemic periodic paralysis (HypoPP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>1:200 000</td>
<td>1:100 000</td>
</tr>
<tr>
<td>Mode of inheritance</td>
<td>Autosomal dominant</td>
<td>Autosomal dominant a</td>
</tr>
<tr>
<td>Onset</td>
<td>First or second decade</td>
<td>Type 1: CACNA1S (1q31–q32)</td>
</tr>
<tr>
<td>Gene (locus)</td>
<td>SCN4A (17q23)</td>
<td>Type 2: SCN4A (17q23)</td>
</tr>
<tr>
<td>Protein (short name)</td>
<td>Skeletal muscle Na⁺ channel α subunit (Na,1.4)</td>
<td>Skeletal muscle Ca⁺⁺ channel α1 subunit (Ca,1.1)</td>
</tr>
<tr>
<td>Mutation effect</td>
<td>Gain of function</td>
<td>Loss of function b</td>
</tr>
<tr>
<td>Paralysis/Myotonia a</td>
<td>Yes/Yes</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Duration of attacks</td>
<td>Short (minutes to hours)</td>
<td>Long (hours to day)</td>
</tr>
<tr>
<td>Triggers</td>
<td>K⁺ intake, fasting, rest after exercise and cold exposure</td>
<td>High-carbohydrate or high-Na⁺ meal and K⁺-lowering diuretics</td>
</tr>
<tr>
<td>Treatment</td>
<td>I: continuous mild exercise, carbohydrate load and β2-mimetics aerosols II: CAI and HCTZ diuretics</td>
<td>I: oral K⁺ intake II: CAI and K⁺-sparing diuretics</td>
</tr>
</tbody>
</table>

a Acquired forms exist: thyrotoxic HypoPP (Asian > Caucasian).

b Some mutations cause a cation leak in the gating pore see [21].

c Disease termed Paramyotonia Congenita whether symptoms are cold-induced.

d CAI may aggravate the symptoms in some HypoPP patients.

CAI, carbonic anhydrase inhibitors; HCTZ, hydrochlorothiazide.
HyperPP is a typical example of transcellular shifts of K\(^+\) caused by mutations in skeletal muscle Na\(^+\) channels. The attacks of HyperPP impact on the daily life of young patients, causing familial and social problems [6]. The episodic nature of the disease, with normal muscle function in between, may complicate the diagnosis. Electrophysiological studies and provocative tests can be useful, although caution should be taken with the latter. Advances in the molecular genetics of channelopathies facilitate the diagnosis, since two mutations of SCN4A account for the majority of HyperPP cases. With more cases documented, genotype–phenotype correlations are emerging, which are essential to decipher the pathophysiology of the diseases caused by Na\(^+\)Chs mutations. Insights into the structure of these channels should lead to the development of compounds that would provide more specific therapies.

**Conflict of interest statement.** None declared.


**References**

1. Bernard C. *An Introduction to the Study of Experimental Medicine*, 1865
Renal tubular acidosis (RTA) is an uncommon disorder; however, the subgroup of isolated familial proximal RTA (pRTA) is exceedingly rare. The term ‘isolated’ pRTA distinguishes these disorders from Fanconi syndrome, in which pRTA is exceedingly rare. The term ‘isolated’ pRTA distinguishes these disorders from Fanconi syndrome, in which peritubular capillary bicarbonate transfer is enhanced in the setting of tubulointerstitial damage.

In the era of molecular biology, how does this model hold up? Are there inherited mutations of the transport proteins that confirm the model? This is indeed in part what was found. ‘Autosomal recessive pRTA with ocular abnormalities’ is, for instance, attributable to homozygous mutations in the gene for kNBC-1 (Figure 1) [2]. Affected patients show pRTA and short stature, glaucoma and cataracts, psychomotor delay and calcification of basal ganglia and corneal opacities.

The human body generates ~50–100 mmol of mineral acid per day. This load must be excreted, to prevent metabolic acidosis. Cells function best at physiological pH; hence it is advantageous for the body to keep pH as constant as possible. The kidney is the only organ equipped to fully excrete the daily acid load, and the proximal tubule is the workhorse of that process. It transports hydrogen ion into the tubular lumen, reabsorbs bicarbonate (Figure 1) and contributes to the excretion of ammonium (NH4+) and titratable acid. The machinery consists of a number of integrated tools (Figure 1): a Na+/H+ exchange protein for hydrogen ion secretion (NHE-3) in the apical cell membrane; maintenance of a low intracellular sodium concentration by the activity of a basolateral Na+/K+-ATPase; a Na+/HCO3−-cotransporter in the basolateral membrane (kNBC-1) to facilitate translocation of bicarbonate to the extracellular fluid; carbonic anhydrases II and IV, which function in the disposition of CO2 (Figure 1).

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