REVIEW ARTICLE

The primary periodic paralyses: diagnosis, pathogenesis and treatment


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Periodic paralyses (PPs) are rare inherited channelopathies that manifest as abnormal, often potassium (K)-sensitive, muscle membrane excitability leading to episodic flaccid paralysis. Hypokalaemic (HypoPP) and hyperkalaemic PP and Andersen-Tawil syndrome are genetically heterogeneous. Over the past decade mutations in genes encoding three ion channels, CACN1AS, SCN4A and KCNJ2, have been identified and account for at least 70% of the identified cases of PP and several allelic disorders. No prospective clinical studies have followed sufficiently large cohorts with characterized molecular lesions to draw precise conclusions. We summarize current knowledge of the clinical diagnosis, molecular genetics, genotype-phenotype correlations, pathophysiology and treatment in the PPs. We focus on unresolved issues including (i) Are there additional ion channel defects in cases without defined mutations? (ii) What is the mechanism for depolarization-induced weakness in Hypo PP? and finally (iii) Will detailed electrophysiological studies be able to correctly identify specific channel mutations? Understanding the pathophysiology of the potassium-sensitive PPs ought to reduce genetic complexity, allow subjects to be stratified during future clinical trials and increase the likelihood of observing true clinical effects. Ideally, therapy for the PPs will prevent attacks, avoid permanent weakness and improve quality of life. Moreover, understanding the skeletal muscle channelopathies will hopefully lead to insights into the more common central nervous system channel diseases such as migraine and epilepsy.

Keywords: Andersen-Tawil syndrome; channelopathy; episodic weakness; periodic paralysis; potassium-sensitive

Abbreviations: ATS = Andersen-Tawil syndrome; CMAP = compound motor action potential; HyperPP = hyperkalaemic periodic paralysis; HypoPP = hypokalaemic periodic paralysis; PMC = paramyotonia congenita; PP = periodic paralysis; K = potassium

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Introduction

Primary periodic paralyses (PPs) are autosomal dominant disorders of ion channel dysfunction characterized by episodic flaccid weakness secondary to abnormal sarcolemmal excitability. Classically, PP is classified as hyperkalaemic (HyperPP) or hypokalaemic (HypoPP) based on serum potassium (K) level or response to K administration (Table 1). Although PP is seldom life-threatening, the attacks produce disability and a majority of affected individuals develop persistent, interattack weakness. Moreover, morbidity and mortality associated with cardiac arrhythmia in a subset of PP patients, those with Andersen–Tawil syndrome (ATS; some authors refer to the disorder as ‘Andersen syndrome’), has yet to be fully appreciated. Although the genotypic spectrum of the PP has expanded over the past decade, molecular lesions in an uncertain proportion of subjects remain unknown.

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Clinical features

Hypokalaemic periodic paralysis (MIM170400)

HypoPP is the most common PP, with a prevalence of ~1:100 000 (Fontaine, 1994). Inheritance is autosomal dominant with reduced penetrance in women (Fontaine, 1994; Elbaz et al., 1995; Fouad et al., 1997; Miller et al., 2004; Sternberg et al., 2001). Approximately one-third of cases may be new dominant mutations (M. Hanna, personal communication). Symptoms typically begin in the first or second decade, attacks of flaccid paralysis usually occurring on awakening in the night or in the early morning. Weakness may be focal or generalized, usually sparing facial and respiratory muscles, and lasting for hours (occasionally days) with gradual resolution. Frequency of individual attacks can vary from daily to a few episodes in a lifetime; attacks often decrease in frequency after age 40. Attacks occur spontaneously or are provoked by prolonged rest after vigorous exercise or a carbohydrate-rich meal on the previous day. Attacks can also be triggered by stress including intercurrent viral illness, lack of sleep, menstruation and specific medications (e.g. beta agonists, corticosteroids and insulin). Many individuals describe a vague prodrome (paraesthesias, fatigue, illness, lack of sleep, menstruation and specific medications) the day prior to an attack. Attacks of weakness in HyperPP usually last 1–4 h (infrequently days), are generalized and triggered by rest after exercise and are K-sensitive. Attacks may also be precipitated by stress and fatigue. Rarely, bulbar and respiratory muscles will be involved in severe paralysis. Interictally, lid lag and eyelid myotonia may be the only clinical signs present. A large proportion of subjects with HyperPP develop a progressive proximal myopathy, similar to HypoPP, which is unrelated to attack frequency (Bradley et al., 1990; Miller et al., 2004) and seen with increasing age (Plassart et al., 1994). Electrical myotonia is found in 50–75% of affected individuals (Plassart et al., 1994; Miller et al., 2004) yet is clinically apparent in <20% (Plassart et al., 1994). Although typically associated with elevated ictal serum K levels, many individuals are normokalaemic during attacks. In such patients K-sensitivity symptoms may be ameliorated by exercising.

Andersen–Tawil syndrome (MIM 170390)

Andersen-Tawil syndrome (ATS), first described in 1971 (Andersen et al., 1971), is characterized by the triad of PP, ventricular ectopy and skeletal anomalies (Tawil et al., 1994; Sansone et al., 1997). Prevalence is unknown but estimated at one-tenth that of HypoPP. Symptomatic onset typically is with episodic weakness in the first or second decade. Intermittent weakness occurs spontaneously or may be triggered by prolonged rest or rest following exertion; permanent proximal weakness often develops. Attack frequency, duration and severity are variable between and within affected individuals and may not correlate with ictal serum K levels, which may be reduced, normal or elevated. ECG manifestations (Fig. 1) include prolongation of the corrected QT interval (QTc), prominent U waves, premature ventricular contractions, ventricular bigeminy and polymorphic ventricular tachycardia. A subset of patients manifests a unique form of ventricular tachycardia, bidirectional ventricular tachycardia, which is characterized by beat-to-beat alternating QRS axis polarity (Fig. 1). While many patients with ventricular ectopy are asymptomatic, others present with palpitations, syncope or rarely cardiac arrest (Tristani-Firouzi et al., 2002). Unlike

Hyperkalaemic periodic paralysis (MIM170500)

Episodic weakness manifests at an earlier age in HyperPP than HypoPP kindreds, most commonly in the first decade. There is high penetrance. The allelic disorder paramyotonia congenita (PMC) presents with muscle stiffness, worsening with activity and cold temperature; affected individuals may have attacks of weakness in addition to muscle stiffness. Episodes of weakness in HyperPP usually last 1–4 h

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<th>Table I Clinical features of the primary PPs</th>
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<td><strong>Age at onset</strong></td>
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<td><strong>Duration of attacks</strong></td>
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<td><strong>Fixed proximal weakness</strong></td>
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<td><strong>Skeletal developmental anomalies</strong></td>
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<td><strong>Response to potassium</strong></td>
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<td><strong>Mutations</strong></td>
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Intracranial K

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Fixed proximal weakness Yes Yes
CACNA1S Mutations Response to potassium Improves weakness Triggers weakness Depends on ictal K
Skeletal developmental anomalies No No Yes
Cardiac arrhythmias No No Yes
Usual triggers Rest after exercise, attacks (Links ness develops independent of the frequency and severity of potassium concentration. Fixed permanent proximal weak-
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other forms of arrhythmia-susceptibility syndromes, many ATS patients remain asymptomatic despite frequent runs of tachycardia (Tristani-Firouzi et al., 2002). Furthermore, there appears to be a lower incidence of syncope and sudden death in ATS compared with other long QT (LQT) syndromes (Tristani-Firouzi et al., 2002). Distinctive physical findings (Fig. 2) include a small mandible, ocular hypertelorism, low set ears, clinodactyly, syndactyly and broad nasal root (Donaldson et al., 2003; Tristani-Firouzi et al., 2002). Short stature, unilateral hypoplastic kidney (Andelfinger et al., 2002), vaginal atresia and brachydactyly (Canun et al., 1999) have been reported. Detailed study has also identified microcephaly, short palpebral fissures, thin upper lip, small hands/feet, residual primary dentition and delayed bone age (Yoon and Ptacek, unpublished).

**Clinical diagnosis**

Diagnosis of PP requires a history of transient episodes of weakness, determination of ictal serum potassium levels, EMG and exclusion of secondary causes. During an attack, weakness is evident either diffusely or in recently exercised muscle groups. Muscle stretch reflexes are usually hypoactive. In primary HypoPP the K level is low during attacks. In HyperPP, K levels may be elevated; however, the K level remains within the normal range in up to 50% of cases (Plassart et al., 1994; Chinnery et al., 2002). The term K-sensitive may be more appropriate since weakness is typically provoked by K administration. HypoPP attacks respond to oral K ingestion; between episodes serum K should be normal. A provocative K challenge may be necessary to determine K-sensitivity (Griggs, 1983).

Assessment of thyroid status is mandatory for diagnosis of HypoPP. Thyrotoxic PP (MIM 188580) is often indistinguishable from HypoPP. All patients without a family history and any patient presenting after age 20 should be assessed for suppressed TSH and elevated free T4 (fT4) or fT3 levels. In thyrotoxic PP the associated hypokalaemia is often profound. There is a predilection, which can be inherited, for men and in particular Asians, although thyrotoxic PP may be seen in all races.

A diagnosis of ATS (Table 3) can be made when an individual has two of the three cardinal features: (i) PP; (ii) ventricular ectopy and (iii) typical ATS facies (Tawil et al., 1994; Sansone et al., 1997; Tristani-Firouzi et al., 2002). However, the phenotypic variability in ATS may obscure the diagnosis in the absence of a family history of all three cardinal features. Therefore, ATS should be considered in any individual presenting with isolated PP or polymorphic ventricular ectopy. A prolonged QU interval or large amplitude U wave may be more sensitive than the QTc interval, which overlaps with the upper limit of normal (Zhang et al., 2005) (Fig. 1). The episodic weakness seen in affected individuals with ATS has been associated with normal, elevated but most commonly, reduced serum K levels (Tawil et al., 1994; Sansone et al., 1997; Tristani-Firouzi et al., 2002).

During an episode of weakness, the compound motor action potential (CMAP) may be reduced, and rarely, absent on motor nerve conduction studies; insertional activity is reduced, fibrillation potentials and positive sharp waves are seen and there is an increased proportion of polyphasic motor unit potentials on needle examination (Engel et al., 1965). Surface and invasive EMG studies document reduced muscle fibre conduction velocity (Links and van der Hoeven, 2000). Intercital clinical electrophysiological testing (Table 2) is
Adapted from Fournier et al., 2004

**Table 2** Electrodiagnostic features of the primary PPs

<table>
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<tr>
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<th>HyperPP (SCN4A)</th>
<th>HypoPP1 (CACN1AS)</th>
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<tr>
<td>Mutation</td>
<td>T704M</td>
<td>RS28H</td>
</tr>
<tr>
<td>EMG pattern</td>
<td>IV</td>
<td>V</td>
</tr>
<tr>
<td>Electrical myotonia</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Short exercise protocol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-exercise myotonic potentials</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Post-exercise CMAP</td>
<td>Increase</td>
<td>No change</td>
</tr>
<tr>
<td>Long exercise protocol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate post-exercise CMAP</td>
<td>Increase</td>
<td>No change</td>
</tr>
<tr>
<td>Delayed post-exercise CMAP</td>
<td>Decrease</td>
<td>Decrease</td>
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Adapted from Fournier et al., 2004

**Table 3** Diagnostic criteria for ATS

1. A clinically definite diagnosis requires two of the following three features:
   - PP
   - Prolonged QTc interval or ventricular ectopy (identified on ECG or Holter)
   - The typical ATS facies including:
     - Low set ears, ocular hypertelorism, small mandible, fifth digit clinodactyly, syndactyly

2. Alternatively, a diagnosis may be made with one of the three features above and an affected family member meeting two of three.

helpful in the diagnosis of PP. Changes in CMAP after exercise may correlate with exercise-induced symptoms (McManis et al., 1986) and channel mutation (Fournier et al., 2004). Myotonia on EMG needle examination occurs in ~75% of individuals with HyperPP and in all patients with PMC; EMG myotonia does not occur in HypoPP. Electrodiagnostic studies at room temperature and after cooling the extremity may be more sensitive for HyperPP and PMC. The long exercise protocol also may detect a delayed decrement in ATS patients (Katz et al., 1999).

Muscle biopsy changes are non-specific in the PP. Tubular aggregates are more commonly seen in ATS. A vacuolar myopathy, resulting from reduplication of the sarcoplasmic reticulum and transverse tubules, may be seen in HypoPP and HyperPP. Such changes were detected in 21 out of 29 (72%) of affected individuals with either HyperPP or HypoPP (Miller et al., 2004). Patients with fixed weakness may have non-specific myopathic changes, with or without vacuolar change.

### Genetics

The PPs are autosomal dominant, have high penetrance and are genetically heterogeneous (Table 1). Family history may be overlooked because of non-penetrance in previous generations and intra-familial variability. Sporadic cases from *de novo* mutations are frequent in HypoPP and have also been documented in HyperPP and ATS.

HypoPP is caused by mutations in the alpha subunits of either the skeletal muscle L-type calcium channel gene *CACN1AS* ([HypoPP1]) (Jurkat-Rott et al., 1994; Ptacek et al., 1994a; Fontaine et al., 1994; Elbaz et al., 1995) or the skeletal muscle sodium channel gene *SCN4A* ([HyperPP2]) (Bulman et al., 1999; Jurkat-Rott et al., 2000; Struyk et al., 2000; Bendahhou et al., 2001; Sternberg et al., 2001). Two of three missense mutations in the calcium channel gene account for up to 70% of HypoPP cases (Fouda et al., 1997; Jurkat-Rott et al., 2000; Davies et al., 2001; Miller et al., 2004) while 10–20% of affected individuals will have a point mutation in the sodium channel gene (Bulman et al., 1999; Jurkat-Rott et al., 2000; Davies et al., 2001; Sternberg et al., 2001; Kim et al., 2004; Miller et al., 2004; Vicart et al., 2004). A small number of definitely affected kindreds do not have a mutation in the calcium or sodium genes and are not linked to these loci. The possibility that HypoPP may be caused by mutations in *KCNE3* (Abbott et al., 2001) has not been substantiated (Sternberg et al., 2003; Jurkat-Rott and Lehmann-Horn, 2004).

Most cases of HyperPP, as well as the allelic disorders paramyotonia congenita and K-aggravated myotonia, are caused by mutations in *SCN4A* (Fontaine et al., 1990; Ptacek et al., 1991, 1992; Rojas et al., 1991; McClatchey et al., 1992a; Heine et al., 1993). The most common are the missense mutations T704M and M1592V (Ptacek et al., 1994a) accounting for 75% of affected individuals (Miller et al., 2004) while other point mutations account for the remainder of affected individuals (McClatchey et al., 1992a; Plassart et al., 1996; Wagner et al., 1997; Bendahhou et al., 1999a, 2000, 2002).

ATS is caused by missense mutations or small deletions (Plaster et al., 2001; Tristani-Firouzi et al., 2002; Ai et al., 2002; Andelfinger et al., 2002; Donaldson et al., 2003; Hosaka et al., 2003) in *KCNJ2*, encoding the inwardly rectifying K channel, Kir 2.1 (Plaster et al., 2001), in approximately two-thirds of the affected individuals ([ATS1] (Plaster et al., 2001; Tristani-Firouzi et al., 2002; Donaldson et al., 2003). The molecular lesion(s) have not been identified in ~30% of subjects including kindreds not linked to *KCNJ2*.

The expression of thyrotoxic PP may be a result of an inherited predisposition that is uncovered by thyrotoxicosis. An initial report of an R83H mutation in the *KCNE3* gene causing thyrotoxic PP (Dias Da Silva et al., 2002) proved erroneous as 1% of healthy controls, in addition to patients affected with familial PP, thyrotoxic PP and PMC have this missense polymorphism in *KCNE3* (Sternberg et al., 2003; Jurkat-Rott and Lehmann-Horn, 2004).

### Genotype–phenotype correlations

No prospective study has followed a sufficiently large cohort with characterized molecular lesions to draw precise conclusions. Intuitively, since the mutations are invariant they cannot completely explain the intrakindred and interkindred phenotypic variations in PP. The marked phenotypic variability in a large Quarter horse pedigree affected by a missense mutation in the equine sodium channel ortholog was attributed to the ratio of mutant and normal sodium channels.
expressed in skeletal muscle (Zhou et al., 1994). Prospective studies as well as further experimental electrophysiology data are necessary to understand the factors that trigger attacks and produce the varying phenotypic severity of human PPs.

What is remarkable is the striking phenotypic heterogeneity evident with discrete sodium channel mutations causing the allelic disorders HypoPP (Bulman et al., 1999; Jurkat-Rott et al., 2000), HyperPP (Fontaine et al., 1990; Cannon et al., 1991; Ptacek et al., 1991), paramyotonia congenita (McClatchey et al., 1992; Ptacek et al., 1992) and K-aggravated myotonia (Heine et al., 1993; Ptacek et al., 1994b; Ricker et al., 1994), in addition to a congenital myasthenic syndrome (Tsujino et al., 2003). Missense mutations in the highly conserved arginine residues (R699 and R672) of the voltage sensing segment 4 (S4) of domain II (DII) are associated with HypoPP (Bulman et al., 1999; Jurkat-Rott et al., 2000). However, four kindreds with mutations in the adjacent R675 residue had clinical features of HyperPP, were always normokalaemic on repeated ictal testing and yet two individuals had inducible hypokalaemia (Vicart et al., 2004). Moreover, there is also a kindred with a P1158S mutation in exon 19 of SCN4A and temperature-dependent shifts of voltage dependence in the sodium channel activation. Affected individuals present with heat-induced myotonia and cold-induced HypoPP (Sugiura et al., 2000). HypoPP may also have an allelic disorder—malignant hyperthermia susceptibility without PP has been described with mutation in CACN1AS (Monnier et al., 1997). All PP patients undergoing surgery should be monitored for malignant hyperthermia-like reactions that may be life-threatening; however, prolonged paralysis post-operatively without the usual signs of malignant hyperthermia (rigidity, marked elevation in CK) is more likely related to the stress of surgery.

There are some useful distinguishing features nevertheless. The largest retrospective series involved 226 patients with characterized molecular lesions for HypoPP1 (42), HyperPP2 (7), HyperPP (81) and PMC (49) providing clinical data for patients with and without identifiable mutations (Miller et al., 2004). Age of onset was earlier and the duration of episodes was longer in HypoPP1 (10 years; ~20 h) versus HyperPP2 (16 years; ~1 h). Earlier age of onset and more severe hypokalaemia were also seen in HypoPP1 patients with the R1239H (7 years; 1.9 mEq/l) CACN1AS mutation versus R528H (14 years; 2.9 mEq/l). In HypoPP1 patients, >70% had fixed proximal weakness compared with none of the HyperPP2 patients. Similarly, in HyperPP cases, there was a younger age of onset, more frequent attacks and shorter duration with T704M (0.8 years; 28/months; 8 h) SCN4A mutation versus M1592V (5 years; 3/month; 89 h). Patients without mutations were slightly atypical with an older age of onset, absence of diet as a trigger and non-specific myopathic changes, rather than a vacuolar myopathy, on muscle biopsy (Miller et al., 2004).

In addition, an EMG study in 51 genetically characterized channelopathy patients with HypoPP1 (13), HyperPP2 (2), HyperPP (12), PMC (16), K aggrivated myotonia (2) and myotonia congenita (6) provides important electrodagnostic clues (Fournier et al., 2004). Needle EMG, post-exercise myotonic potentials and change in CMAP amplitude after short and long exercise protocols revealed five distinct electrophysiological patterns that could be correlated with patient groups based on known mutations. This protocol differentiated HypoPP1 patients with the R528H CACN1AS mutation from HyperPP patients with a T704M SCN4A mutation (Table 2) (Fournier et al., 2004). It remains to be seen whether these patterns will differentiate between patients with HypoPP1 and HypoPP2.

Currently, individuals with clinically defined ATS are phenotypically indistinguishable, regardless of the presence (ATS1) or absence of KCNJ2 mutation (Tristani-Firouzi et al., 2002; Donaldson et al., 2003). Phenotypic variability is high, only 60% of affected individuals manifest the complete triad while ~80% express two of the three cardinal features (Tristani-Firouzi et al., 2002). This variability is evident even within kindreds carrying the identical KCNJ2 mutation (Tristani-Firouzi et al., 2002; Andelfinger et al., 2002; Donaldson et al., 2003). Non-penetrance may be seen in up to 20% of individuals with a defined Kir2.1 mutation (Tristani-Firouzi et al., 2002; Andelfinger et al., 2002; Donaldson et al., 2003).

Pathophysiology

All forms of familial PP share a common final mechanistic pathway: aberrant depolarization, which inactivates sodium channels and renders the muscle fibre electrically inexorable (Lehmann-Horn et al., 2002). Differences in attack frequency, severity and precipitating factors probably reflect which channel gene is affected, and the specific alterations in mutant channel function. Other factors, such as relative expression level or variations in other determinants of cellular excitability must also have an influence, since phenotypic variability is observed in unrelated kindreds with the same mutation or even among affected members in a single family.

Based on early microelectrode studies in PP, an increase in sodium permeability was hypothesized (McComas et al., 1968). However, membrane depolarization was later shown to be caused by abnormal inactivation of voltage-gated sodium channels (Lehmann-Horn et al., 1987). Direct measurement of channel activity in isolated membrane patches from myotubes (Cannon et al., 1991) as well as in muscle fibres from patients with HyperPP (Lehmann-Horn et al., 1991) showed the impaired inactivation. Operationally, this defect in mutant channel gating creates a gain-of-function, and the increased sodium current will excessively depolarize affected muscle. Over 20 sodium channel (SCN4A) mutations with gain-of-function defects due to impaired inactivation, or in some cases enhanced activation, have been established as the cause of HyperPP or PMC (Lehmann-Horn and Jurkat-Rott, 1999; Cannon, 2002). Electrophysiological correlates in affected patients are thought to be the reduced ictal CMAP (Engel et al., 1965), slowing of muscle fibre conduc
The primary periodic paralyses

velocity (Zwarts et al., 1988; Links et al., 1994), and decrement on the long exercise protocol (McManis et al., 1986; Kuntzer et al., 2000; Fournier et al., 2004).

In HyperPP and PMC, gain-of-function mutations occur in highly conserved amino acids on the cytoplasmic face of the channel (Ptacek et al., 1991; Rojas et al., 1991), the inactivation gate (McClatchey et al., 1992b) or the voltage sensor (S4) of DIV (Ptacek et al., 1992; Lerche et al., 1996) resulting in impaired fast (Cannon et al., 1991; Wagner et al., 1997; Bendahhou et al., 1999b) or slow inactivation (Cummins and Sigworth, 1996; Hayward et al., 1999; Ruff and Cannon, 2000) and, therefore, persistent increased sodium current and sarcolemmal depolarization. It is the degree of depolarization and inactivation of normal sodium channels that dictates whether the muscle fibre membrane is hyperexcitable (myotonia) or inexcitable (weakness).

The mechanism for depolarization-induced attacks of weakness in HypoPP is not understood. Missense mutations in the a1 subunit of the L-type calcium channel (Jurkat-Rott et al., 1994; Ptacek et al., 1994a), or less commonly in the voltage-gated sodium channel (Bulman et al., 1999; Jurkat-Rott et al., 2000), cause HypoPP. Curiously, for both channel types the mutations occur in highly conserved arginine residues in the voltage-sensing segments. The calcium channel mutations cause a loss-of-function manifest as reduced current density (Lapie et al., 1996) and slower activation (Morrill et al., 1998). This observation does not readily explain the episodes of depolarization, weakness and hypokalaemia. In vitro, muscle fibres from patients with HypoPP depolarize in low K solution (Rüdel et al., 1984). A study on fibres biopsied from a patient with the R528H calcium channel mutation detected a reduction in ATP-sensitive K current (Tricarico et al., 1999), which is more easily tied to depolarization with hypokalaemia and suggests a secondary channelopathy stemming from altered calcium homeostasis. The sodium channel mutations associated with HypoPP2 enhance inactivation to produce a net loss-of-function defect (Jurkat-Rott et al., 2000; Struyk et al., 2000; Bendahhou et al., 2001). This behaviour is the converse of the gain-of-function changes observed in HyperPP, but the mechanism linking this defect to depolarization and hypokalaemia in HypoPP remains obscure.

Kir2.1 channels stabilize the resting membrane potential in skeletal and cardiac muscle, and contribute significantly to the most terminal repolarization phase of the cardiac action potential (Plaster et al., 2001; Tristani-Firouzi et al., 2002). The majority of KCNJ2 mutations exert a dominant-negative effect on channel function (Plaster et al., 2001; Lange et al., 2003; Donaldson et al., 2004). Most mutant channels traffic normally to the cell surface, but fail to conduct appropriately (Bendahhou et al., 2003). Many mutations alter the binding of phosphatidylinositol 4,5 bisphosphate, which is an important regulator of Kir2.1 channel function (Lopes et al., 2002; Donaldson et al., 2003). While limited in vivo data are available, reduced Kir2.1 channel function in skeletal muscle may cause sustained membrane depolarization, leading to failure of action potential propagation and flaccid paralysis (Cannon, 2002). In the heart, altered Kir2.1 function may prolong the most terminal phase of repolarization, leading to delayed after-depolarizations and Na+/Ca2+-dependent triggered activity (Tristani-Firouzi et al., 2002; Mlake et al., 2003). A broad range of possible molecular candidates for ATS2 includes genes homologous to Kir2.1 and gene products that modulate Kir2.1 channel expression, trafficking and function. The development of an animal model of ATS will probably advance our understanding of the skeletal and cardiac muscle pathophysiology.

Animal models

Equine hyperPP is a dominantly inherited disorder characterized by episodic weakness associated with elevated serum potassium and muscle stiffness due to a single point mutation in S3/DIV of the skeletal sodium channel alpha subunit (Rudolph et al., 1992) causing impaired fast inactivation (Cannon et al., 1995). Mouse models such as knock-in, knock-out and cDNA transgenics may provide more accessible alternatives to the equine model, allow specific questions to be addressed in vivo, and well characterized mouse models can then be used for screening possible therapeutic agents. There are no published reports of viable mouse models to date; the Kir2.1 knock-out is lethal (Zaritsky et al., 2000).

Natural history

The natural history of the PPs has not been documented by prospective studies. Published case series suggest the highest frequency of attacks in the teenage years followed by a decreasing attack frequency with increasing age in both HyperPP and HypoPP. Approximately two-thirds of the patients will develop progressive fixed weakness (Miller et al., 2004) unrelated to frequency of episodic weakness (Links et al., 1990); risk factors other than a specific molecular lesion have yet to be determined. Estimated at one-tenth the prevalence of HypoPP, there is even less appreciation for the natural history of ATS, although there is some evidence to suggest that the cardiac arrhythmias may be less likely to degenerate into a fatal arrhythmia than occur with other LQT syndromes. Many unanswered questions remain, including the relationship of K to the cardiac and skeletal muscle manifestations, the risk of fixed weakness and the outcome of the cardiac arrhythmias. The presence of Kir2.1 in the CNS raises the question of whether there may be a CNS phenotype.

Treatment

The management of PP has been symptomatic and behavioural; affected individuals learn to avoid precipitating triggers through lifestyle and dietary modification. Patients with hypokalaemic attacks eat frequent small meals to avoid large carbohydrate loads. In contrast, those with
hyperkalaemic attacks stay away from K rich foods, medications that increase serum K (e.g. spiranolactone) and fasting.

There are no randomized clinical trials in the acute management of paralytic attacks, which targets normalization of serum K levels. For HypoPP, the administration of oral K (20–30 mEq/l orally every 15–30 min until serum K is normalized) is usually sufficient for resolution of weakness. Patients may take oral potassium (15–30 mEq) at the beginning of an attack to alleviate or shorten the episode. Conversely, patients with HyperPP will continue with mild activity or ingest sweets to prevent or shorten attacks. Beta agonist inhalers (1–2 puffs of 0.1 mg salbutamol or albuterol) attenuate hyperkalaemic attacks (Ricker et al., 1989).

Anecdotal evidence showed benefit with sodium restriction and potassium supplementation (Conn et al., 1957) in HypoPP as well as with acetazolamide (125–1000 mg/day) treatment in HyperPP (McArdle, 1956) and HypoPP (Resnick et al., 1968). Dichlorphenamide (50–200 mg/day) is another carbonic anhydrase inhibitor that reduces attack frequency (Dalakas and Engel, 1983). These observations led to the only randomized, double blind clinical trial in PP. Dichlorphenamide, when compared with placebo, significantly reduced attack frequency in patients with HyperPP and HypoPP (Tawil et al., 2000). HyperPP patients, i.e. those with SCN4A mutations, may have been excluded from the trial because of reports of worsening of attacks with acetazolamide treatment (Torres et al., 1981; Sternberg et al., 2001) although there are other reports of patients with SCN4A mutations deriving benefit with acetazolamide (Davies et al., 2001; Venence et al., 2004; Vicart et al., 2004). A clinical trial is currently underway comparing treatment with dichlorphenamide and acetazolamide on the primary outcome, attack frequency. Despite this, <50% of affected individuals are prescribed prophylactic medication (Tawil et al., 2000). The observation that prophylactic treatment improves fixed weakness (Giggs et al., 1970; Dalakas and Engel, 1983) is also under investigation in the randomized controlled trial.

The mechanism of action of carbonic anhydrase inhibitors is unclear and is independent of carbonic anhydrase inhibition. In vitro studies show that carbonic anhydrase inhibitors relieve weakness in K⁺-deficient rats through activation of calcium-activated K channels (Tricarico et al., 2000, 2004) rather than direct inhibition of carbonic anhydrase.

No prospective, randomized therapeutic trials have been completed in ATS. Anecdotal evidence suggests that like HyperPP and HypoPP, carbonic anhydrase inhibitors may be effective in the prevention of attacks of PP. K-wasting diuretics and other drugs that prolong the QT interval may be hazardous. There is very limited data demonstrating clear efficacy of any antiarrhythmic agent, alone or in combination, to control the frequent ventricular ectopy manifested by ATS patients. While many ATS subjects are treated empirically with beta-blockers, there is little evidence that beta-blockers alter the frequency of ventricular tachycardia. The primary question as to whether asymptomatic patients with frequent runs of non-sustained ventricular tachycardia are better off without therapy remains to be determined from natural history cohort studies. For patients with tachycardia-induced syncope or aborted sudden cardiac death, an implantable cardioverter-defibrillator is a prudent option (Chun et al., 2004). Kir2.1 channels are paradoxically sensitive to external K⁺ concentration, increasing their conductance with increasing external K⁺. Likewise, the hERG K channel is also paradoxically sensitive to external potassium and this effect was recently exploited to shorten the QT interval in LQT2 subjects with hERG mutations by combining spironolactone and oral K supplementation (Etheridge et al., 2003). Prospective studies are needed to determine whether a similar approach may benefit ATS patients.

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The primary periodic paralyses


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Appendix

This report summarizes the findings of an International Conference on the Pathogenesis and Treatment of the PPs (Rochester NY, October 31, 2004). The conference was generously supported by an NIH conference grant IR13 NS050966-01 as well as the Muscular Dystrophy Association and the Association Française contre les Myopathies.

Members of the International Meeting on the Pathogenesis and Treatment of the PPs listed alphabetically:

Anthony Amato (Brigham and Women’s), Robert Barchi (Thomas Jefferson University), Richard Barohn (University of Kansas), Dennis Bulman (Ottawa Health Research Institute), Domenico Tricarico (University of Bari), Stephen Cannon (University of Texas Southwestern), Emma Ciafaloni (University of Rochester), James Cleland (University of Rochester), Patrick Cochran (Periodic Paralysis Association), Marinos Dalakas (NINDS, NIH), Magnus Dias DaSilva (UCSF), Nick Davis (Queen Elizabeth Hospital, UK), Erik Ensrud (Noran Neurological Clinic), Doreen Fialho (Institute of Neurology, UK), Bertrand Fontaine (Pitie-Salpetriere, France), Tracey Graves (Institute of Neurology), Robert C. Griggs (University of Rochester), Angelika Hahn (London Health Sciences Ctr, Canada), Michael Hanna (Institute of Neurology, UK), Lawrence Hayward (University of Massachusetts), Barbara Herr (University of Rochester), Ellen Hess (Johns Hopkins), Joanna Jen (UCLA), Bethan Lang (Weatherall Institute of Molecular Medicine, UK), Jake Levitt (Taro Pharamaceuticals, Inc), Thera Links (Hospital Groningen, Netherlands), Giovanni Meola (University of Milan, Italy), Hiroshi Mitsumoto (Columbia Presbyterian), Louis Ptacek (UCSF), Ming Qi (University of Rochester), Goran Rakocivic (NINDS, NIH), Seward Rutkove (Beth Israel Deaconess), Robert Ruff (Cleveland VA Medical Center), Valeria Sansone (University of Milan, Italy), David Saperstein (University of Kansas), Damien Sternberg (Pitie-Salpetriere, France), Randall Stewart (NINDS, NIH), Arie Struyk (Massachusetts General Hospital), Rabi Tawil (University of Rochester), Charles Thornton (University of Rochester), Martin Tristani-Firouzi (University of Utah), Shannon Venance (London Health Sciences Center, Canada), Savine Vicart (Pitie-Salpetriere, France), Grace Yoon (UCSF).