

Muscle channelopathies: does the predicted channel gating pore offer new treatment insights for hypokalaemic periodic paralysis?

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## **Abstract**

Hypokalaemic periodic paralysis (hypoPP) is the archetypal skeletal muscle channelopathy caused by dysfunction of one of two sarcolemmal ion channels, either the sodium channel Nav1.4 or the calcium channel Cav1.1. Clinically, hypoPP is characterised by episodes of often severe flaccid muscle paralysis, in which the muscle fibre membrane becomes electrically inexcitable, and which may be precipitated by low serum potassium levels. Initial functional characterisation of hypoPP mutations failed to adequately explain the pathomechanism of the disease. Recently, as more loss of positive charge pathogenic mutations in the S4 segments of either channel have been identified, the hypothesis that an abnormal gating pore current may be important has emerged. Such an aberrant gating pore current has been identified in mutant Nav1.4 channels and has prompted potentially significant advances in this area. The carbonic anhydrase inhibitor acetazolamide has been used as a treatment for hypokalaemic periodic paralysis for over 40 years but its precise therapeutic mechanism of action is unclear. In this review we summarise the recent advances in understanding of the molecular pathophysiology of hypoPP and consider how these may relate to the reported beneficial effects of acetazolamide. We also consider potential areas for future therapeutic development.

## **Abbreviations List**

**hypoPP: hypokalaemic periodic paralysis**

**CA: carbonic anhydrase**

**IRK: inward rectifying potassium**

## Introduction

Hypokalaemic periodic paralysis (hypoPP) is an autosomal dominant neuromuscular disorder characterised by episodes of flaccid paralysis of skeletal muscle in association with reduced serum potassium levels. Paralysis commonly lasts for hours to days but in some patients it can be weeks to months before full muscle strength is restored. Attacks usually occur during the night or early morning and are often precipitated by rest after strenuous exercise or by a large carbohydrate load. The age of onset is typically in the teenage years but can be up to the third decade (Miller *et al.*, 2004). Occasionally, severe respiratory compromise is reported (Kil & Kim, 2009; rzel-Hezode *et al.*, 2009). Cardiac muscle is not primarily affected by the disease. However, if the reduction in serum potassium is profound there may be associated ECG changes such as flattened ST segments, u waves, or a prolonged QT interval, which may predispose to significant arrhythmias (Kil & Kim, 2009; Hecht *et al.*, 1997; Kim *et al.*, 2005).

In the initial years of the disease, in between the episodes of paralysis, patients often function independently and muscle strength examination may be unremarkable. However, the subsequent development of a severe fixed disabling proximal myopathy occurs in a significant number of cases (Biernacki & Daniels A.P., 1934; Fouad *et al.*, 1997; Sternberg *et al.*, 2001; Miller *et al.*, 2004).

The carbonic anhydrase inhibitor acetazolamide was first used in 1962 to lower the elevated potassium levels associated with paralytic attacks in hyperkalaemic periodic paralysis (McArdle, 1962). A few years later, despite seeming counterintuitive in terms of potassium balance, acetazolamide was also reported to be an effective prophylactic agent in hypokalaemic periodic paralysis (Resnick *et al.*, 1968). A subsequent observational

study suggested acetazolamide may also improve inter-attack muscle strength in some patients (Griggs *et al.*, 1970).

Acetazolamide rapidly became the main treatment for hypoPP, although clear randomised control trial level evidence that it is effective and prevents muscle weakness is not yet available. Despite its current popularity as a therapeutic agent, the disease specific mechanism of action is not understood. Several possible mechanisms have been investigated which we consider here. Furthermore, acetazolamide is also considered to be effective in certain brain channelopathies such as episodic ataxia. It is therefore possible that insights into the molecular basis of acetazolamide's beneficial effect in muscle channelopathies may be relevant to brain channelopathies.

## **Genetics**

HypoPP is caused by point mutations in two sarcolemmal ion channel genes, CACNA1S that codes for the dihydropyridine receptor Cav1.1 (Fontaine *et al.*, 1994; Ptacek *et al.*, 1994; Jurkat-Rott *et al.*, 1994) and SCN4A that codes for the alpha sub-unit of the skeletal muscle voltage gated sodium channel Nav1.4 (Bulman *et al.*, 1999). Both channels have similar structures consisting of a single ion selective pore formed by the configuration of four domains (Fig 1C), each domain containing six alpha-helical transmembrane segments. To date, all but one of the identified mutations causing hypoPP are point mutations that neutralise positively charged arginine residues in one of the S4 segments of either channel (Ptacek *et al.*, 1994; Jurkat-Rott *et al.*, 1994; Bulman *et al.*, 1999; Wang *et al.*, 2005; Jurkat-Rott *et al.*, 2000; Bendahhou *et al.*, 2001; Sternberg *et al.*, 2001; Kim *et al.*, 2004; Chabrier *et al.*, 2008; Matthews *et al.*, 2009; Ke *et al.*, 2009) (Fig 1A and 1B).

The most common of these voltage sensor mutations are R528H and R1239H in CACNA1S and together account for approximately 70-80% of cases (Fouad *et al.*, 1997; Sternberg *et al.*, 2001; Miller *et al.*, 2004; Matthews *et al.*, 2009). A significant minority are due to mutations in SCN4A. We recently reported that arginine voltage sensor mutations account for 90% of cases of hypoPP, indicating that disruption of the voltage sensor is crucial to the pathogenesis of disease (Matthews *et al.*, 2009).

### **Pathomechanisms**

Attacks of paralysis occur in conjunction with reduced serum potassium levels in hypoPP. In vitro studies of muscle fibres from individuals affected by hypoPP have been shown to paradoxically depolarise when placed in low potassium solution (in contrast to muscle fibres from normal controls which hyperpolarise) (Ruff, 1999; Rudel *et al.*, 1984). Early functional studies of the voltage sensor mutations demonstrated reduced current density and minor shifts in the voltage dependence of inactivation or slower kinetics of activation (Struyk *et al.*, 2000; Kuzmenkin *et al.*, 2002; Lapie *et al.*, 1996; Morrill & Cannon, 1999) suggesting that an overall loss of channel function may be important. However, this mild loss of function did not explain the paradoxical depolarization seen in native muscle and did not explain how the episodes of lowered extracellular potassium were triggered.

Recently, a gating pore current caused by loss of the interaction between the positively charged arginine residues of the voltage sensor of Nav1.4 and the surrounding negatively charged residues in the S1/2/3 transmembrane segments has been identified. This gating pore current is quite independent from the ion selective alpha pore (Sokolov *et al.*,

2007;Struyk & Cannon, 2007;Sokolov *et al.*, 2008;Struyk *et al.*, 2008). Expression studies of the R672G SCN4A mutation demonstrated permeability for monovalent cations through the gating pore while studies of the R669H SCN4A mutation indicated proton selectivity. The precise consequences of this gain of channel function on muscle cell homeostasis and sarcolemmal excitability are not yet fully understood. It is suggested that movement of protons and/or sodium ions via the gating pore may disrupt pH homeostasis and leads to intracellular sodium accumulation via activation of several ion transporters including the sodium-hydrogen anti-port exchanger (see Fig 2)(Struyk *et al.*, 2008;Jurkat-Rott *et al.*, 2009). However, the cause of the paradoxical membrane depolarisation in low potassium solution remains unclear.

Muscle fibre resting membrane potential ( $V_{\text{REST}}$ ) is controlled by the membrane permeability to  $K^+$  ions. It has been suggested that inhibition of the outward component of the inward rectifying potassium channels could account for the abnormal membrane response to low serum potassium and also for the lowered serum potassium itself due to intracellular accumulation of potassium(Hofmann & Smith, 1970;Ruff, 1999).

Furthermore, barium which blocks inward rectifying potassium channel current (Standen & Stanfield, 1978) can produce reduced twitch force in the skeletal muscles of mammals in vitro in low potassium solution (Gallant, 1983). Reduced ATP dependant potassium channel (a subgroup of IRK channel) current has also been identified in vitro from muscle biopsies of hypoPP patients(Tricarico *et al.*, 1999). The aberrant inward depolarizing gating pore current has recently been shown to contribute to the probability of the membrane paradoxically depolarising in the presence of low potassium solution and also to the reduced outward current component of the IRK channels (Jurkat-Rott *et*

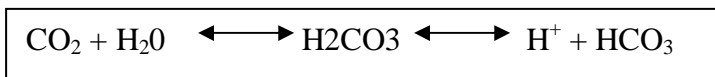
*al.*, 2009; Struyk & Cannon, 2008). However, it is not clear why the potassium conductance should be reduced by dysfunction of the voltage sensors of Cav1.1 or Nav1.4. One possible explanation is that a protonic gating pore current causes an acidic intracellular environment and IRK channels are known to be inhibited at this pH (Struyk & Cannon, 2008).

The only mutation associated with HypoPP that does not neutralise a positive charge in an S4 segment is the CACNA1S V876E substitution in the S3 segment of domain III (Ke *et al.*, 2009). Potentially, introduction of a negative charge in this way could be hypothesised to disrupt the integrity of the interaction between the S3 segment and the voltage sensor (S4) and also produce a gating current. However S4 segment mutations of SCN4A were not excluded in this kindred and functional studies will be crucial to clarify its significance.

## **Mechanisms of action of acetazolamide**

### **Carbonic Anhydrase Inhibition**

Carbonic anhydrase is an enzyme that catalyses the reversible reaction converting carbon dioxide and water into protons and bicarbonate.



Acetazolamide is a sulphonamide that inhibits carbonic anhydrase (CA) and it is generally considered that its main therapeutic mechanism of action in hypoPP is somehow linked to this capacity. Inhibition of CA in the renal tubules by acetazolamide leads to increased urinary loss of bicarbonate, sodium and some potassium with a resultant metabolic acidosis (Fig 3). It remains unclear how this alteration of pH could

reduce paralytic attacks or prevent the development of myopathy. One study did examine the effect of pH on the R669H SCN4A mutation and pH on the R672H/G SCN4A mutations expressed in a HEK cell system. The deleterious effects of the histidine substitutions could be ameliorated by a more acidic pH whereas the glycine substitution was insensitive to alterations in pH. The authors proposed this may predict that those hypoPP patients with a glycine substitution would not benefit from acetazolamide (Kuzmenkin *et al.*, 2002). We have reviewed all published cases of patients with glycine substitutions; i.e. R528G, R1239G, or R672G. In total only eight cases could be identified in whom the response to acetazolamide was reported in sufficient detail (Kil & Kim, 2009; Kim *et al.*, 2007; Sternberg *et al.*, 2001) It is notable that none of these individuals reported benefit and five actually reported a detrimental response.

### **Carbonic Anhydrase Isoenzymes**

At least 14 isoenzymes of CA exist in humans. Different isoenzymes are preferentially expressed in the cytosol, cell membranes or mitochondria of different tissues. Each isoform demonstrates a different degree of catalytic activity and affinity for sulfonamides (Clare & Supuran, 2006; Supuran & Scozzafava A, 2000) see Table 1 reproduced with permission from (Supuran & Scozzafava A, 2000).

The subcellular localisation of several isoforms have been studied in animal models and shown to be present at variable levels in the sarcolemma and sarcoplasmic reticulum of skeletal muscle (Wetzel & Gros, 1998; Wetzel *et al.*, 2007; Scheibe *et al.*, 2008). The presence of different isoforms of CA in skeletal muscle raises interesting questions about how the contribution of each isoform may influence CA treatment response and how this



might be influenced by the proposed proton permeable gating pore. Intracellular isoforms of CA can only be reached by the lipophilic membrane permeable sulphonamides. Hydrophilic sulphonamides such as acetazolamide or the alternative carbonic anhydrase inhibitor dichlorphenamide, that is also used in hypoPP, cannot easily cross the sarcolemma and would not be expected to have any significant direct effect on the intracellular isoforms. This suggests any benefit derived from acetazolamide relies on inhibition of extracellular carbonic anhydrase or carbonic anhydrase on the extracellular surface of the membrane.

### **Acetazolamide and activation of sarcolemmal calcium activated potassium channels**

[K<sub>Ca2+</sub>]

Tricarico et al used the potassium depleted rat as an animal model of hypoPP to explore the hypothesis that the mechanism of action of acetazolamide and other carbonic anhydrase inhibitors were not exclusively related to their inhibition of CA. A dose dependant increase of calcium activated potassium channel [KCa<sup>2+</sup>] activity and restoration of the serum potassium levels to within the normal range was observed in the muscle fibres of potassium depleted rats in whom treatment with acetazolamide prevented insulin induced attacks of paralysis (Tricarico *et al.*, 2000; Tricarico *et al.*, 2004). The ability of acetazolamide to enhance the sarcolemmal conductance of potassium seems particularly relevant when considered in light of the studies discussed that implicate inhibition of IRK channel conductance in the pathomechanism of hypoPP.

### **Effects of acetazolamide on inter-attack weakness**

The reported clinical benefit of acetazolamide in preventing or improving inter-attack weakness has also been explored using the K depleted rat model. Vacuoles are a common morphological finding in primary and secondary hypokalaemic periodic paralysis. They are considered to represent localised swelling and vacuolation of the t-tubules secondary to increased osmolarity caused by the local accumulation of ions or metabolites (including lactate). The rat model demonstrated a vacuolar myopathy and an increased efflux of lactate from muscle fibres in vitro. Muscle biopsies from rats treated with acetazolamide demonstrated significantly reduced vacuoles and lactate efflux (Tricarico *et al.*, 2008).

These observations are particularly interesting when considered in light of the proposed proton leak described in hypoPP. Accumulation of intracellular protons could produce an increased efflux of lactate by stimulating the proton linked monocarboxylate transporter (Fig 2). Potentially this pathway may partly explain the reports of acetazolamide ameliorating inter-attack muscle weakness.

### **Potential for new future therapeutic options**

Advances in genetics and functional studies have expanded our understanding of the disease mechanism of hypoPP and allowed some insight into the pathways through which acetazolamide may modulate disease expression. However, many questions remain unanswered and in particular whether alternative treatment options could be viable (Table 2).

A largely unexplored area is the role that inhibition of different isoforms of CA expressed in skeletal muscle may have in treatment response. If a proton permeable gating pore does make a significant contribution to the pathogenesis of hypoPP and if inhibition of IRK channels by an acidic intracellular environment contributes to this, then the activity (and inhibition) of intracellular CA may be particularly important. Studies are needed that can ascertain the role of each skeletal muscle isoform in more detail to determine if drugs which target specific isoforms of CA could be tolerated and effective.

The aberrant cation pathway predicted by hypoPP mutations is itself another potential target for therapeutic consideration. The identification of compounds which can block this pathway without impinging on the essential movement of the voltage sensor for channel gating could be new therapeutic options.

However, it may be that the most promising approach will be to reconsider potassium channel openers. The recognition that there is reduced sarcolemmal potassium conductance prompted several studies on the use of potassium channel openers. Two examined the effect of such compounds in vitro using muscle fibres from hypoPP patients. The first reported a repolarisation of depolarised fibres and an increase in twitch force (Grafe *et al.*, 1990) and the second described a partial restoration of  $K_{ATP}$  channel conductance with cromakalim (Tricarico *et al.*, 1999). Another study compared the use of the potassium channel opener pinacidil to placebo in four hypoPP patients and found that it was effective in improving muscle strength in two (Ligtenberg *et al.*, 1996). There have been no follow up larger scale studies in this area. The potassium channel activators preliminarily investigated do not act exclusively on skeletal muscle and side effects may

complicate their use. The identification of skeletal muscle specific potassium channel openers could be important.

While the precise pathomechanism of hypokalaemic periodic paralysis is not fully resolved the best molecular targets for treatment will continue to be uncertain. However, the discovery of the gating pore current has provided new insights into the molecular pathophysiology of hypoPP. These insights are relevant to understanding the mechanisms of action of carbonic anhydrase inhibitors and to developing new therapies.

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Isozyme	Catalytic activity(CO <sub>2</sub> hydration)	Affinity for Sulphonamides	Subcellular location
CA I	Low(10% of that of CA II)	Medium	Cytosol
CA II	High	Very high	Cytosol
CA III	Very low(1% of that of CA II)	Very low	Cytosol
CA IV	High	High	Membrane bound
CA V	Moderate-high	High	Mitochondria
CA VI	Moderate	Medium-low	Secreted into saliva
CA VII	High	Very high	Cytosol
CA VIII	Acatalytic	Not measured	Probably cytosolic
CA IX	High	Unknown	Membrane bound
CA X	Acatalytic	Not measured	Unknown
CA XI	Acatalytic	Not measured	Unknown
CA XII	Low	Unknown	Membrane bound
CA XIII	Probably high	Unknown	Unknown
CA IV	Low	Unknown	Membrane bound

Table 1: Higher vertebrate  $\alpha$ -CA isozymes, their relative CO<sub>2</sub> hydrase activity, affinity for sulphonamide inhibitors and subcellular location. Reproduced with permission from (Supuran & Scozzafava A, 2000).

Pathomechanism	Target pathway	Potential therapy
Disrupted intracellular pH homeostasis	Possible role of intracellular carbonic anhydrases	Isoform specific and membrane permeable carbonic anhydrase inhibitors
Gating pore leak	Aberrant cation permeability	Gating pore “blockers”
Inhibition of IRK channels	Reduced sarcolemmal potassium conductance	Potassium channel activators

Table 2: Proposed mechanisms of disease for hypoPP and possible potential future therapeutic developments.

## Figure Legends

Fig 1 A: diagrammatic representation of Cav1.1 with voltage sensor mutations highlighted. B: diagrammatic representation of Nav1.4 with voltage sensor mutations highlighted. C: configuration of four domains in each channel to form a single ion selective pore.

\*There is evidence R675G has a gating pore opened by depolarisation. This is in contrast to the gating pore which is open at hyperpolarising potentials for the other SCN4A mutants studied to date. The phenotype of the R675G/Q/W mutants also differs being one of potassium sensitive normokalaemic periodic paralysis.

Fig 2: An aberrant current permeable to protons could stimulate the NHE and NBC transporters with a resultant increase in intra-cellular sodium ions. Stimulation of the monocarboxylate transporter would result in increased lactate efflux from the cell which has been proposed as contributory to vacuolar formation (see text)

Fig 3: Acetazolamide(ACZ) inhibits the carbonic anhydrase(CA) present in the tubular lumen preventing the conversion of  $\text{H}_2\text{CO}_3$  to  $\text{CO}_2$  and  $\text{H}_2\text{O}$ .  $\text{H}_2\text{CO}_3$  dissociates to  $\text{H}^+$  and  $\text{HCO}_3^-$ . Bicarbonate is lost in the tubular lumen producing a metabolic acidosis. Within the proximal tubular cell itself ACZ blocks the CA preventing the conversion of  $\text{CO}_2$  and  $\text{H}_2\text{O}$  to  $\text{H}^+$  and  $\text{HCO}_3^-$ . The reduction in protons reduces the re-absorption of sodium ions which are excreted in the urine.

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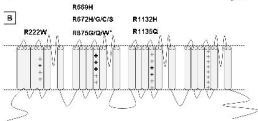
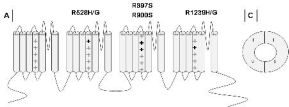
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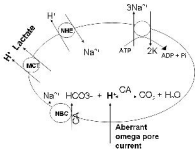
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MCT: monocarboxylate transporter NHE: Sodium hydrogen anti-port exchanger  
 NBC: sodium dependant bicarbonats transporter CA: carbonic anhydrase

