

Treatment of Neuromuscular Channelopathies: Current Concepts and Future Prospects

James C. Cleland*[†] and Robert C. Griggs[†]

*Department of Neurology, Waikato Hospital, Hamilton, New Zealand 3214 and [†]Department of Neurology, University of Rochester, Rochester, New York 14627

Summary: Our understanding of the molecular pathogenesis of the neuromuscular ion channelopathies has increased rapidly over the past two decades due to the identification of many of the genes whose mutation causes these diseases. These molecular discoveries have facilitated identification and classification of the hereditary periodic paralyses and the myotonias, and are likely to shed light on acquired ion channelopathies as well. Despite our better understanding of the pathogenesis of these disorders, current treatments are largely empirical and the evidence in favor of specific therapy largely anecdotal. For periodic paralysis, dichlorphenamide—a carbonic anhydrase inhibitor—has been shown in a controlled trial to prevent attacks for many patients with both hypokalemic and hypokalemic periodic paralysis. A second trial, comparing dichlorphenamide with acetazolamide versus placebo, is currently in progress. For

myotonia, there is only anecdotal evidence for treatment, but a controlled trial of mexiletine versus placebo is currently being funded by a Food and Drug Administration–orphan products grant and is scheduled to begin in late 2008. In the future, mechanism-based approaches are likely to be developed. For example, exciting advances have already been made in one disorder, myotonic dystrophy-1 (DM-1). In a mouse model of DM-1, a morpholino antisense oligonucleotide targeting the 3' splice site of *CLCN1* exon 7a repaired the RNA splicing defect by promoting the production of full-length chloride channel transcripts. Abnormal chloride conductance was restored, and myotonia was abolished. Similar strategies hold potential for DM-2. The era of molecularly-based treatments is about to begin. **Key Words:** Therapy, channelopathy, ion-channel, electrophysiology.

INTRODUCTION

The study of neuromuscular ion-channel disorders (“channelopathies”) is rapidly evolving. Although the prototype disorders myotonia congenita and paramyotonia congenita were discovered over 100 years ago, our understanding of the molecular pathogenesis has vastly expanded (almost in exponential fashion) during the past 20 to 30 years. This progress is primarily due to identification of causal genes coupled with advances in molecular technology such as heterologous expression systems and patch-clamping technology. We are now at the forefront of advances that will eventually complete our understanding of the pathophysiology of channelopathies, thus opening the door to more effective and targeted therapies for these disorders. Once considered rare, even disorders as common as migraine and epilepsy are now linked to ion-channel dysfunction, and the spectrum

of ion-channel diseases is ever-expanding (Table 1). Moreover, the identification of defects of abnormal RNA splicing leading to reduced ion channel expression (e.g., myotonic dystrophy), and acquired defects of ion-channel function in diseases once believed to be pathophysiologically distinct (e.g., critical-illness myopathy), further illustrate the complexity and diversity of this group of disorders.

This chapter outlines current understanding of ion-channel pathophysiology and existing neuromuscular channelopathy treatments, and discusses emerging and potential future treatment approaches. A detailed discussion of the pathophysiology of neuromuscular channelopathies is beyond the scope of this review, and the reader is directed to several more detailed reviews on the subject^{1–4} and a recent review on clinical trial design in neurologic channelopathies.⁵

NEUROMUSCULAR CHANNELOPATHIES: BASIC CONCEPTS

Neuromuscular channelopathies are due to dysfunctional membrane excitability in either skeletal muscle or

Address correspondence and reprint requests to: James Cleland, Department of Neurology, Waikato Hospital, Private Bag 3200, Hamilton, New Zealand. E-mail: clelandj@waikatodhb.govt.nz.

Table 1. Examples of Neuromuscular Channelopathies

	Ion Channel	Gene	Reference
Inherited disorders			
Periodic paralysis			
Hyperkalemic	Na _v 1.4	<i>SCN4A</i>	2
Hypokalemic	Ca _v 1.1 or Na _v 1.4	<i>CACNA1S</i> or <i>SCN4A</i>	2
Other PP	K _v 3.4	<i>MiRP2</i> (?)	14
Andersen-Tawil syndrome	K _{ir} 2.1	<i>KCNJ2</i>	31
Myotonic dystrophy	CLC-1	<i>DMPK</i>	16
Nondystrophic myotonia			
Myotonia congenita (Dominant and recessive)	CLC-1	<i>CLCN1</i>	1
Paramyotonia congenita	Na _v 1.4	<i>SCN4A</i>	32
Neuromyotonia	Na _v 1.7	<i>KCNA1</i>	28
Neuromyotonia with benign neonatal convulsions	K _v 7.2	<i>KCNQ2</i>	30
Familial primary Erythromelalgia	Na _v 1.7	<i>SCN9A</i>	33
Congenital myasthenic syndromes			
	AchR,		34
	Na _v 1.4	<i>SCN4A</i>	35
Central core disease	RyR1	<i>RyR1</i>	36
Malignant hyperthermia			
Susceptibility			
Acquired disorders			
Autoimmune			
AINMT	K _v 1.1		37
LEMS	Ca _v 2.1		38
Toxic/metabolic			
Critical-illness myopathy (?)	Na _v 1.4 (?)		29, 39

AINMT = autoimmune neuromyotonia; LEMS = Lambert-Eaton myasthenic syndrome.

neurons. Fundamentally, dysfunctional ion-channels alter membrane excitability thresholds, either by inherited or acquired defects. Excitability may be either reduced (e.g., periodic paralysis) or enhanced (e.g., myotonic disorders). Generally speaking, inherited channelopathies alter transmembrane ionic currents via one or more of the following mechanisms: 1) altered gating kinetics (e.g., leftward shift of sodium-channel inactivation gating in hypokalemic stimuli (hypoPP) due to *SCN4A* mutations), 2) reduced channel expression due to defective post-transcriptional splicing mechanisms (e.g., abnormal RNA splicing in myotonic dystrophy), or 3) decreased ion-channel expression due to either enhanced mRNA degradation during post-translational processing or reduced chaperone-mediated transport to the muscle membrane (e.g., R894X *CLCN1* recessive myotonia congenita). Acquired defects are more diverse, but are most commonly based on an immune, antibody-mediated mechanism. The inherited channelopathies will be discussed in detail as follows, whereas acquired disorders are discussed elsewhere.⁴

Although the fundamental concept of altered membrane excitability due to defective ion-channel function has already been extensively investigated, the relationship between genotype and phenotype is complex and, in many cases, it is poorly defined. For example, penetrance is variable in periodic paralysis due to sodium channel mutation (often reduced in females), and considerable phenotypic variability may be present among kindreds

with the same mutation. This variability is probably in part explained by genetic elements (e.g., modifying genes) as well as nongenetic factors (e.g., circulating hormones or metabolites) that may further modify phenotype; however, in most cases, these factors remain to be defined. Further data on the natural history of these disorders and genotype–phenotype correlations will be valuable in developing new treatments for these disorders.

CURRENT TREATMENT OF NEUROMUSCULAR CHANNELOPATHIES

Periodic paralysis

Existing treatments for neuromuscular channelopathies are largely empiric and based almost exclusively on anecdotal experience. Since the late, 1960s when the carbonic anhydrase inhibitor acetazolamide was found to blunt or in some cases completely abolish periodic paralysis (PP) attacks, similar agents (e.g., dichlorphenamide) have been used with similar results.⁶ The relative effectiveness of acetazolamide and dichlorphenamide for both prevention of attacks and the prevention or improvement of “fixed” weakness in both hyperkalemic stimuli (hyperPP) and hypoPP are currently under study in a randomized clinical trial (clinicaltrials.gov). However, despite their widespread use, the therapeutic mechanism(s) remain incompletely understood. It is possible that the effect is directly related to carbonic anhydrase inhibitory

or kaliuretic effects, or alternatively, to their ability to open BK-type K^+ channels.⁷ Furthermore, as well as lowering serum K^+ that could benefit hyperPP, acetazolamide also prevents K^+ ingress into muscle, which could benefit hypoPP.^{8,9} Based on evidence of a postassium channel-opening effect of carbonic anhydrase inhibitors (CAIs), other specific potassium channel openers (e.g., cromakalim) have been studied in PP. Although these have improved contractile force in fibers of muscle biopsies from hypoPP patients,¹⁰ an *in vivo* therapeutic effect remains to be proven.

In addition to CAIs, treatment of PP typically involves either potassium replacement (hypoPP) or attempts to reduce serum potassium by enhancing cellular uptake with either inhaled beta agonist or glucose/insulin therapy (hyperPP). Intravenous potassium-replacement protocols are also empiric and can be potentially hazardous, given that rapid fluxes in serum potassium levels may occur with intracellular to extracellular shifts, whereas oral potassium-replacement strategies are usually safer, while still efficacious.

Despite considerable progress in our current understanding of PP pathophysiology, the question of whether altered serum K^+ during PP attacks is cause or effect thereof remains largely unanswered. Although total body potassium is probably normal in genetically-defined and thyrotoxic PP, in contrast with secondary causes of PP (such as hyperaldosteronism, which causes chronic K^+ deficit), abnormal intracellular K^+ shift occurs during PP attacks.¹¹ Why episodes are typically triggered by hyperkalemic or hypokalemic stimuli is unclear, but there is a growing body of evidence implicating alterations in “anomalous” (inwardly-rectifying) potassium (IR_K) currents. This is supported by the following observations: barium intoxication (an agent that blocks inwardly rectifying potassium channels) causes a flaccid paralysis similar to a PP attack.¹² Furthermore, the normal coupling of the muscle-membrane potential to the K-reversal potential becomes uncoupled in the setting of hypokalemia in barium-treated muscle, an effect that is potentiated by insulin.³ Second, Ruff¹³ demonstrated reduced inward-rectification K^+ currents in muscle from patients with hypoPP due to an R528H *CACNA1S* mutation, and mutations in the inwardly-rectifying $K_{ir}2.1$ channel cause Andersen-Tawil syndrome, which is a rare disorder with PP attacks that are clinically indistinguishable from other causes of PP. Third, a less common and controversial cause of periodic paralysis (and possibly also a risk factor for thyrotoxic periodic paralysis) is mutation of the potassium channel, *KCNE3* subunit MinK-related peptide 2 (MiRP2). However, whether this is a pathogenic mutation or a benign polymorphism remains to be established, with up to 15 to 20% of PP cases being negative for genetic testing for known *SCN4A* and *CACNA1S* mutations, thus other loci are undoubtedly

linked to PP.^{2,14} Fourth and finally, others have found reduced inward-rectifying ATP-sensitive K^+ -channel (K_{ATP}) current in muscle biopsies of patients with PP. These channels are metabolically regulated, have a high density in many tissues (e.g., pancreatic islet cells), and are closely regulated by hormones, such as insulin, which provide an attractive hypothesis to explain the link between PP attacks and carbohydrate intake.¹⁵

However, despite significant advances in our understanding of the potential link between reduced IR_K currents and PP attacks, many questions remain unanswered. For example, how do mutations in sodium or calcium channels (which cause the majority of PP) alter IR_K currents? Why are PP attacks precipitated by exercise? Why is the therapeutic response to CAIs so variable? (Some patients worsen, others improve, and others still initially improve, but then the therapeutic effect attenuates).

Myotonic disorders: nondystrophic myotonia (myotonia congenita and paramyotonia congenita), and myotonic dystrophy (types I, II)

The nondystrophic myotonias (NDM) are disorders of either chloride channels (i.e., myotonia congenita [MC]) or sodium channels (i.e., paramyotonia congenita, [PMC]). In NDM, exercise-related muscle stiffness and cramping pain are typical symptoms, but generally, fixed weakness is not. By contrast, weakness rather than stiffness is predominant in the myotonic dystrophies (type 1 associated with CTG repeat in *DMPK* gene on chromosome 19, and type 2 with CCTG repeat in *ZNF9* gene on chromosome 3). Myotonic dystrophy is also associated with extramuscular manifestations, including muscle wasting, cardiomyopathy, and diabetes. While clinically and genetically distinct, nondystrophic and dystrophic myotonic disorders share elements of a common pathogenesis; both disorders result in at least some degree of decreased chloride conductance. In the case of NDM, mutations in *CLCN1* (the gene encoding the CLC-1 muscle chloride channel) can result in a nonfunctional CLC-1 protein, accelerated degradation of mutant *CLCN-1* mRNA transcripts during post-transcriptional processing, or defects in chaperone-mediated CLC-1 protein transport to the sarcolemma. On the other hand, the genetic mutation in myotonic dystrophies causes a more extensive “spliceopathy” that affects numerous and diverse genes, reflecting the more diverse manifestations of myotonic dystrophy. The mutation in DM1 is an expanded CTG-repeat (CUG^{exp}) in the 3' untranslated region (3' UTR) of a protein-kinase encoding gene (*DMPK*) that produces an mRNA that exhibits a “toxic gain of function” effect. It is retained in the nucleus where it adversely affects alternative splicing of many genes controlled by a group of proteins in the muscleblind (MBNL) family, one being *CLCN1*, and another the insulin receptor. This is reviewed elsewhere.¹⁶ Reduced MBNL protein-mediated

alternative splicing of *CLCN1* mRNA transcripts in a mouse model of myotonic dystrophy leads to excessive inclusion of exon 7a, resulting in a truncated and non-functional CLC-1 protein. Mice expressing CUG^{exp} demonstrate myotonia on EMG, and have a 70 to 80% reduction in chloride conductance (a 75% reduction is sufficient to produce myotonia in humans). In these mice, the myotonic phenotype can be at least partially reversed by the overexpression of MBNL protein, consistent with an indirect effect via a splicing defect rather than a direct effect of CUG^{exp} on *CLCN-1* transcription. This rescue is still effective even after myotonia is clinically evident, indicating that the spliceopathy is a dynamic and potentially reversible process, even once established. In DM2, the pathogenesis is similar, but distinct in that the toxic RNA is an expanded tetranucleotide repeat (CCUG^{exp}), and arises in an intronic region of *ZNFN9*. This intronic repeat is then excised from the parent transcript during post-transcriptional processing, whereupon it exerts its toxic effect directly. In other respects, the downstream effects of both mutations on MBNL-mediated alternative RNA splicing are similar, presumably reflecting the similarities in phenotype between DM1 and DM2.

From a pharmacologic perspective, and based on the fact that myotonia is due to repetitive and inappropriate opening of sodium channels, agents that reduce sodium channel opening frequency or duration of opening should be effective in alleviating myotonia. This is indeed borne out in practice. Anticonvulsants such as phenytoin and carbamazepine block sodium channels in a use-dependent fashion (i.e., they preferentially inhibit rapidly and repetitively opening sodium channels), and are variably effective in myotonia. However, because the repetitive firing frequency of sodium channels in myotonic runs is lower than that in epileptic phenomena, these agents are probably less effective in myotonic disorders than in epilepsy. The class IB anti-arrhythmic agents (e.g., mexilitene, a lidocaine derivative) are variably effective, also blocking sodium channels in a use-dependent fashion, but they have a higher affinity for depolarized Na⁺ channels. The explanation for the observation that there is considerable heterogeneity in response to mexilitene in patients with MC and PMC is unclear. In the case of PMC, it is probably in part due to variations in the degree of use-dependent block that depends on whether the mutation is in the inactivation particle (III-IV linker), voltage-sensor (IVS4), or some other part of the Na⁺ channel.¹⁷ Both anticonvulsants and class IB anti-arrhythmics are effective on myotonia in both NDM and DM, although they have a more limited role in DM due to potential cardiac toxicity. They do not seem to alter the natural history of either of these disorders. In PMC/PP overlap syndromes, although they prevent myotonia they do not appear effective in preventing paralytic attacks. On the other hand, class IC

anti-arrhythmic agents (such as propafenone) may hold promise as being effective against both myotonia and paralysis, based on a single report of a patient with PMC due to T1313M *SCN4A* mutation in which both PP and electrodiagnostic abnormalities both improved with propafenone treatment.¹⁸ However, whether propafenone is more effective than mexilitene in the wider clinical setting, or whether its clinical efficacy is mutation-specific requires more investigation.

FUTURE THERAPEUTICS IN NEUROMUSCULAR CHANNELOPATHIES

General concepts

The multiple and distinct channelopathy pathomechanisms previously described preclude the “several diseases, one strategy” approach. First, the rarity and phenotypic heterogeneity of individual channelopathies make placebo-controlled randomized trials difficult, if not impossible. Second, their phenotypic and genotypic heterogeneity likely explain the diverse treatment responses among individuals of different kindreds, yet carrying the same mutation, and sometimes even in the same kindred with the same mutation. Thus, assessment of therapeutic efficacy for even a single form of PP can be challenging, and probably has limited utility in the wider clinical setting unless consistent differences in treatment response allow reasonable prediction of individuals’ therapeutic response *a priori*. One approach that is inherently attractive in channelopathy treatment trials is the use of the controlled, multiple crossover trial, either implemented in single form as an “n-of-1” design (synonyms: single patient trial, treatment optimization trial), or as the more commonly used multiple-crossover trial. In the former design, the patient acts as his or her own control and treatment and placebo (or two treatments in direct comparison with each other) are randomly switched for a predetermined number of iterations to determine whether there is an observable therapeutic effect in that individual. This paradigm has been successfully used in other areas of medicine (e.g., asthma and fibromyalgia), and also in neurology (e.g., nicotine in autosomal dominant nocturnal frontal lobe epilepsy, a disorder caused by mutations of a nicotinic acetylcholine receptor).¹⁹ This design is attractive to patients and physicians who are more likely to participate in trials in which there is a tangible benefit to themselves, which improves recruitment in an otherwise rare disease, and at the same time optimizes treatment for the individual. Although the more conventional randomized, blinded, multiple-crossover trial can also be used, it is subject to the potential problem of low sensitivity in detecting treatment response heterogeneity among individuals due to phenotypic variability of the disease (e.g., due to different mutations, or modifying genes), as the cohort is analyzed as a whole. An alternative,

and perhaps more useful approach is to combine multiple independent n-of-1 trials using hierarchical Bayesian models;²⁰ however, this is statistically complex and harder to administer. Thus, there is no “perfect” trial design in channelopathies, but rather the design must be tailored to the question posed.

Experimental concepts

Molecular-based approaches are likely to have major influence in channelopathy therapeutics, and exciting advances have already been made in related disorders. For example, in a mouse model of myotonic dystrophy, a morpholino antisense oligonucleotide (AON) targeting the 3' splice site of *CLCN1* exon 7a repaired the splicing defect by promoting the production of full-length *CLCN1* transcripts. The chloride conductance was restored, and myotonia was abolished.²¹ Although the pathophysiology of myotonic dystrophy is distinct, these findings have wider implications for neuromuscular channelopathies: 1) AON therapy can be successfully delivered without viral vectors but by direct injection into muscle with electroporation, 2) the spliceopathy can be corrected even once the disease is symptomatic, and 3) specific downstream effects of spliceopathy can be potentially targeted with this approach. Whether it will be effective in NDM (or even PP) is unknown; however, there is some evidence to suggest that it may be. For dominant MC, the production of mutant *CLCN1* transcripts probably exerts its dominant negative effect by forming nonfunctional CLC-1 heterodimers with wild-type channel subunits. “Knockdown” of mutant *CLCN1* transcripts with AON therapy might partially reverse this effect, and may promote formation of a higher proportion of wild-type CLC-1 channels, thus potentially restoring chloride conductance. For recessive MC, the situation is more complicated because most mutations result in the production of nonfunctional channels via missense, nonsense, or premature termination codons (a defect not readily amenable to AON therapy). On the other hand, the technique of *trans*-splicing, in which a ribozyme is used to facilitate splicing of its 3'-exon to a target mRNA sequence to allow restoration of a fully functional mRNA transcript, may hold promise in recessive myotonia congenita. This technique has been used on a canine mutant chloride channel mRNA transcript, and despite a low level of repair efficiency (approximately 1%), up to 18% of cells were found to have detectable chloride currents.²² Whether or not this technique can be applied to an *in vivo* animal model of the disease, and thence to humans, remains to be seen. Furthermore, whether oral AON therapy is possible in channel disorders also remains to be seen. It has, however, recently been successfully used in myasthenia gravis.²³

There are other areas of potential therapeutic interest that exist in PP. The effect of nongenetic factors in modifying PP phenotype is illustrated by thyrotoxic PP. Such individuals do not carry known mutations in so-

dium or calcium channel genes, yet thyrotoxicosis produces a clinical and electrodiagnostic phenotype virtually indistinguishable from those with primary hypoPP. However, once euthyroid, PP attacks typically resolve, yet the electrodiagnostic abnormalities persist, albeit attenuated.²⁴ Furthermore, thyrotoxic patients without PP demonstrate larger declines in compound muscle action potential amplitude than healthy controls, suggesting a susceptibility factor (possibly genetic) that predisposes such individuals to thyrotoxic PP. The implications of these observations are that hormonal status or other metabolic factor(s) may substantially modify the PP phenotype, and that hormonal (or perhaps even dietary) manipulation could offer a novel and hitherto unexplored avenue for therapy. Once the susceptibility factor(s) for TPP has been identified, perhaps it will become more clear which hormone(s) might be appropriate targets for therapy.

Finally, defects in the molecular trafficking of ion channel proteins from endoplasmic reticulum to the cell membrane have been identified in certain ion-channel disorders. In recessive myotonia congenita, voltage-clamping studies in human embryonic kidney (Hek) cells have in some cases demonstrated minimal or no reduction in chloride conductance,²⁵ indicating these mutated channels are still at least partially functional, and raising the possibility that defects of trafficking to the sarcolemma might be one cause of recessive MC. For the *CLCN1* mutations F413C and A513V (both recessive), defects in transport from endoplasmic reticulum to the Golgi system have now been identified. The defect might be due to either defective protein folding that prevents chaperoning, or impaired protein stability, or both.²⁶ Agents that are able to facilitate chaperoning (“pharmacologic chaperones”) have been studied in cystic fibrosis, a defect of an apical cellular chloride channel that regulates cellular salt and water homeostasis. In the most common cystic fibrosis mutation, $\Delta F508$, defective folding leads to a protein that is retained in the ER. This defect is at least partially reversible using pharmacologic chaperones,²⁷ but whether chaperones could rescue the myotonic phenotype in recessive MC is a question that warrants further investigation.

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