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Commentary

Repurposing of sodium channel antagonists as potential new anti-myotonic drugs

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ABSTRACT

Myotonia is often a painful and disabling symptom which can interfere with daily motor function resulting in significant morbidity. Since myotonic disorders are rare it has generally proved difficult to obtain class I level evidence for anti-myotonic drug efficacy by performing randomized placebo controlled trials. Current treatment guidance is therefore largely based on anecdotal reports and physician experience. Despite the genetic channel heterogeneity of the myotonic disorders the sodium channel antagonists have become the main focus of pharmacological interest. Mexiletine is currently regarded as the first choice sodium channel blocker based on a recent placebo controlled randomized trial. However, some patients do not respond to mexiletine or have significant side effects limiting its use. There is a clinical need to develop additional antimyotonic agents. The study of Desaphy et al. is therefore important and provides in vitro evidence that a number of existing drugs with sodium channel blocking capability could potentially be repurposed as anti-myotonic drugs. Translation of these potentially important in vitro findings into clinical practice requires carefully designed randomized controlled trials. Here we discuss Desaphy's findings in the wider context of attempts to develop additional therapies for patients with clinically significant myotonia.

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Introduction

Myotonia, delayed muscle relaxation after forced contraction, can be seen in numerous neuromuscular conditions. It is the central feature however of the myotonic disorders including myotonia congenita, paramyotonia congenita, sodium channel myotonia, and myotonic dystrophy types 1 and 2. Although these disorders share myotonia as a dominant clinical feature they are phenotypically and genetically distinct (see Table 1).

In the 1980s a persistent sodium current not seen in healthy muscle was identified in the muscles of patients with paramyotonia congenita (Lehmann-Horn et al., 1987, 1981). The identification of this current ultimately led to the recognition of SCN4A as the causative gene (Koch et al., 1991; Ptacek et al., 1991). In separate experiments, reduced sarcolemmal chloride conductance was recorded in myotonic goats and humans (Bryant, 1969; Lipicky et al., 1971) and later mutations identified in the CLCN1 gene in patients with myotonia congenita (George et al., 1993; Koch et al., 1992). Reduced chloride conductance is also recognized as the pathomechanism for myotonia in myotonic dystrophy although these disorders are multisystem due to defects in RNA processing (Mankodi et al., 2002).

As our knowledge of these disorders has expanded over time we now know that these two individual mechanisms, persistent sodium current and reduced chloride conductance, are responsible for the sarcolemmal excitability that occurs in myotonic disorders whereby the sarcolemma spontaneously and repetitively depolarizes after the cessation of a neurogenic stimulus. This would at first perhaps suggest that pharmacological agents may have to target these detrimental effects individually. Historically many potential therapies were tried however based only on the aim of treating the symptom of myotonia (regardless of cause) and it is intriguing that sodium channel blockers have triumphed as an effective agent in all the myotonic disorders.

The evolution of sodium channel blockers as anti-myotonic agents

Although the identification of causative gene and understanding of the mechanisms that contribute to myotonia in all the myotonic disorders is relatively new the diseases have been classified clinically for over a century. The profuse electrical activity recorded in those with myotonia was at first thought to be neurogenic. Brown and Harvey however showed that myotonia continued in the muscles of myotonic goats who had been curarized (Brown & Harvey, 1939). Wolf also demonstrated myotonia persisted in those who received spinal anaesthesia but could then be abolished by the addition of quinine. These observations suggested myotonia arose from the muscle itself or neuromuscular

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Table 1
Summary of the myotonic disorders.

Myotonic disorder	Pertinent clinical features	Causative gene	Defective ion channel	Mechanism of myotonia
Paramyotonia congenita	Episodes of myotonia and variable weakness affecting face, hands > legs exacerbated by cold and exercise.	SCN4A	Nav1.4	Persistent sodium current
Sodium channel myotonia	Episodes of myotonia without weakness affecting face, hands, legs. Variable exacerbation from cold and potassium. Warm up phenomena and muscle hypertrophy may be present.	SCN4A	Nav1.4	Persistent sodium current
Myotonia congenita	Episodes of myotonia with or without weakness affecting legs > arms. Cold exacerbation less severe. Warm up phenomena typically present. Muscle hypertrophy common.	CLCN1	ClC-1	Reduced Cl-conductance
Myotonic dystrophy type 1	Multisystem disorder including myotonia, distal myopathy, cataracts, frontal balding, endocrine dysfunction.	DMPK	ClC-1	Reduced Cl-conductance
Myotonic dystrophy type 2	Multisystem disorder including myotonia, proximal myopathy, and cataracts.	ZNF9	ClC-1	Reduced Cl-conductance

junction and led him and others to trial quinine as a treatment for myotonia with some success (Wolf, 1936) although cinchonism could be troublesome and later studies found it to be much less beneficial (Leyburn & Walton, 1959). In the 1950s Geschwind postulated myotonia to be an independent process produced by the membrane of excitable muscle cells after cessation of nerve stimulus and extrapolated the membrane stabilizing effect of procainamide on cardiac muscle to suggest an alternative treatment for myotonia (Geschwind & Simpson, 1955). Aside from quinine and procainamide other trialled treatments included ACTH, prednisone (Leyburn & Walton, 1959), phenytoin (Aichele et al., 1985), disopyramide (Finlay, 1982), and N-propyl-ajmalin (Birnberger et al., 1975). The benefits and side effects of each were variably reported without any clear advantage of any particular agent. It was increasingly recognized however that the majority had membrane stabilizing effects and lessons in selecting drugs were frequently extrapolated from their use stabilizing the cardiac muscle membrane as anti-arrhythmics. It was also noted that their ability to stabilize the membrane was based on their sodium channel blocking properties well before the genetic identification of the voltage gated sodium channel Nav1.4 as a major contributor to the myotonic disorders. Although alternative approaches have been considered including acetazolamide (Ferriby et al., 2006; Griggs et al., 1978; Trudell et al., 1987), nifedipine (Grant et al., 1987) and tricyclics (Gascon et al., 1989) sodium channel blockers became established as the main pharmacological target.

By the mid-1980s another sodium channel blocker with anti-arrhythmic properties the lidocaine derivative tocainide was emerging as a more consistently effective treatment for myotonia (Aichele et al., 1985; Ricker et al., 1980; Rudel et al., 1980; Streib, 1986; Streib, 1987). However numerous reports of serious adverse reactions led to its use being discontinued (Dunn et al., 1988; Oliphant & Goddard, 1988; Volosin et al., 1985). More recent reports have supported the use of propafenone (Alfonsi et al., 2007), flecainide (Desaphy et al., 2013; Rosenfeld et al., 1997), carbamazepine (Caietta et al., 2013; Lyons et al., 2010) and mexiletine (Statland et al., 2012).

Mexiletine

A major disadvantage of early studies was that they frequently included a mix of myotonic disorders categorized on a clinical not genetic basis, were not well designed and often used multiple agents consecutively without any washout period. In more recent times it has remained difficult to conduct large scale studies due to the rarity of the disorders. In addition, although there are multiple useful tools available it remains troublesome to accurately quantify myotonia, a sign which naturally fluctuates daily and can be influenced by multiple factors including diet, exercise and temperature. As recently as 2009 there were still no randomized controlled drug trials of any therapy for myotonia and a Cochrane review concluded that there was no evidence to support any of the currently used treatments (Trip et al., 2006). Despite this, clinical experience frequently favoured mexiletine over the other potential sodium channel blockers and since that review two positive treatment trials have been reported using mexiletine. The first in myotonic dystrophy type 1 (Logigian et al., 2010) and the second in non-dystrophic myotonia including those with both sodium and chloride channel disorders (Statland et al., 2012). Whilst both demonstrated good efficacy for mexiletine and no serious adverse events making it the only anti-myotonic agent with randomized controlled trial data to support its use Desaphy et al. highlight several limitations of everyday clinical practice (Desaphy et al., 2014). These include: a lack of efficacy for a significant number, and a lack of tolerability for some. The most frequent side effects reported were gastrointestinal disturbance. Although caution is advised in those with pre-existing cardiac disease or symptoms suggestive of cardiac disease, no significant cardiac events occurred in either study. Probably the most crucial limitation that Desaphy describes is the limited accessibility to supply with manufacture of mexiletine having discontinued in many countries including the US and the UK. This has resulted in mexiletine having to be imported often with special arrangements that carry an additional administrative and cost burden. This places patients and myologists at a further disadvantage with many non-specialist centres unable to meet these requirements adding to the already limited access to the only proven anti-myotonic treatment.

Alternative sodium channel blockers

As such Desaphy et al. (2014) highlight the need for alternatives to mexiletine and investigate the potential benefits of other drug treatments using both a rat model of myotonia induced by injecting the chloride channel blocker anthracen-9-carboxylic acid, and HEK293 cells expressing wild type human isoform Nav1.4 channels. Using these in vivo and in vitro systems they compared mexiletine to other drugs reported to have benefits as anti-myotonic agents: flecainide, propafenone and carbamazepine and other sodium channel blockers: orphenadrine, riluzole, lubeluzole and epo-CBZ. They conclude that all drugs tested in vivo display anti-myotonic properties and demonstrated greater potency than mexiletine. They compare the potency of use-dependent inhibition of Nav1.4 in vitro with the ED50 for anti-myotonic effect in vivo of each drug illustrating a strong correlation between the two with the exception of propafenone and carbamazepine (and it's metabolites), the discrepancies for these drugs being attributed to pharmacokinetics in vivo. In simple terms they have demonstrated that in vitro testing of sodium channel blockers can be a reliable (although not infallible) predictor of an effective anti-myotonic treatment in vivo. In addition they calculate and compare the dose of drug used in their rat model with doses used in humans concluding that the anti-myotonic dose for all drugs tested, including those which have not yet been trialled in humans as specific anti-myotonic agents should be within safe variables with some caution advised for lubeluzole because of a concern over prolonged QT interval. Desaphy argues for the exploration of the drugs tested as alternative agents to mexiletine. Given the rarity of myotonic disorders and the difficulty in conducting clinical trials the ability to select the best candidates to put forward for such a limited resource is imperative and Desaphy et al. very nicely begin to prioritise the options with this work.

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