EDITORIAL

Introduction to *The Journal of Physiology*'s Special Issue on Neurological Channelopathies

Brian Robertson
Deputy Editor in Chief, The Journal of Physiology

It gives me special pleasure to welcome readers to this *Journal of Physiology* Special Issue on Channelopathies, and offer my thanks to the our distinguished organising editors, Professors Dimitri Kullmann and Stephen Waxman, for their efforts in putting this exciting and important issue together. Almost no area of modern physiology brings together so many different disciplines working together as the effort to understand the channelopathies. From structural biologists, biophysicists and neuroscientists to clinicians (and not forgetting the all-important sufferers and their families), these disparate groups can all bring their expertise and tools to bear on unravelling the puzzles offered by this wide range of diseases and disorders.

Here is an extract from a letter of William Harvey, writing to the physician John Vlackveld in 1657:

Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature by careful investigation of cases of rarer forms of disease.

Channelopathies provide a superb example of this, and have become one of the most interesting areas of research over the last couple of decades. And from a teaching point of view, these disorders offer a fascinating route into physiology. I've used the sad stories behind the unravelling of the molecular basis of Jervell and Lange-Nielsen syndrome or the true life cases of congenital insensitivity to pain to get biochemistry and even physics undergraduates 'into' potassium and sodium channels. Students and the general public (and I hesitate to say this, but researchers also) are fascinated by detective stories and diseases. Channelopathy research encompasses both.

A scientific introduction to this Special Issue on channelopathies, provided by the two investigators who were the driving force behind it, Dimitri Kullmann and Steve Waxman, invites readers to think. They concisely describe high points of the progress made since the first ion channel mutations were linked to monogenic neurological disease, posit that other non-monogenic disorders of excitability may arise from interplay of multiple genes including those that encode ion channels, and then put some timely issues and emerging concepts on the table.

The subsequent articles are from a wide variety of expert 'channelopathologists' describing a selection of diseases from nerve and muscle.

Wimmer *et al.* (2010) focus on the axon initial segment, which contains a high density of key voltage gated ion channels, and describe how it may become a hotspot for epileptogenesis. Still on epilepsy, Rajakulendran *et al.* (2010) describe the results of their studies of mutations in *CACNA1A*, the gene encoding the principal subunit of the P/Q calcium channel. Mutations here underlie episodic ataxia type 2 (EA2). Interestingly, some patients with episodic ataxia and epilepsy have *CACNA1A* mutations. The authors conclude that mutations in *CACNA1A* that confer a loss of P/Q-type channel function are associated with episodic ataxia and epilepsy. Meisler and her colleagues (2010) point out that sodium channel mutations can play a key role in human epilepsies, with several hundred mutations in *SCN1A* encoding the sodium channel $Na_V1.1$ being the most common genetic cause of inherited and sporadic epilepsy. On the same topic, Catterall *et al.* (2010) propose a unified loss-of-function hypothesis for the spectrum of epilepsy syndromes caused by genetic changes in $Na_V1.1$ channels, where mild impairment of sodium channel function underlies febrile seizures, and at the other end of the spectrum, with complete loss of function leading to intractable epileptic seizures. Of course, epilepsies may also be caused by changes in receptor-channel function, and Macdonald *et al.* (2010) give a review of how mutations in several inhibitory $GABA_A$ receptor subunit genes (*GABRA1*, *GABRB3*, *GABRG2* and *GABRD*) also leads to different types of epilepsy, ranging from childhood absence epilepsy to generalized epilepsy with febrile seizures. The mutations in $GABA_A$ genes vary, and can lead to alterations in receptor-channel function directly or trafficking and folding problems. Still in the brain, Daniela Pietrobon (2010) discusses experiments with transgenic mice, which serve as a model for familial hemiplegic migraine type 1 (FHM1). FHM1 is a subtype of migraine associated with aura, and is caused by mutations in $Ca_V2.1$ (P/Q-type) Ca^{2+} channels.

Of course, it is not only the CNS that shows channelopathies. Skeletal muscles are also affected, and this issue has two reviews on the current state of play of research here. Matthews & Hanna (2010) focus on hypokalaemic periodic paralysis (hypoPP), with a discussion of potential clinical therapies. Steve Cannon (2010) describes in some detail the missense mutations at arginine residues in S4 voltage sensors of of the skeletal sodium channel $Na_V1.4$, which lead to a 'gating pore current' causing hypoPP.

Cregg *et al.* (2010) review how a careful study of channelopathies helps us to understand pain pathways, and perhaps offer clues to novel therapeutics to deal with the major health problems associated with pain.

Last but not least, Steve Waxman's group (in a Special Issue related paper, Estacion *et al.* 2010) show some of their results with automated patch clamp technology, employed by them to screen previously undescribed mutations in the $Na_V1.7$ sodium channel (S211P), which causes erythromelalgia.

There is a lot in this Special Issue, for a wide range of readers; I hope that you will enjoy and learn as much from the articles as I did.

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