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Commentary

Acquired and genetic channelopathies: *In vivo* assessment of axonal excitability☆

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ABSTRACT

Neuronal or axonal ion channel function can be impaired or altered in a number of disorders, such as acquired (autoantibody-mediated, toxic, and metabolic) and genetic channelopathies, and even neurodegenerative (motor neuron disease) or inflammatory diseases (multiple sclerosis, immune-mediated neuropathies). When specific channels are affected, axonal/neuronal excitability primarily alters according to original function of the corresponding channels. Separately, in the 1990s, axonal excitability testing was developed to assess ion channel function, membrane potential, and passive membrane properties non-invasively in human subjects. Using this technique, numerous papers on altered axonal excitability in a variety of disorders have been published since 2000. In a recent issue of *Experimental Neurology*, Park et al. demonstrated changes in peripheral axonal excitability in limbic encephalitis and acquired neuromyotonia with anti-voltage gated potassium channel antibodies. Unexpectedly, the results were not consistent with those caused by simple potassium channel blockade, suggesting that multiple other factors contribute to altered axonal excitability. In contrast it was reported that patients with episodic ataxia type 1 (genetic channelopathy with mutation of Kv1.1 channel gene) show prominent excitability changes exactly compatible with fast potassium channel blockade. This commentary aims to highlight findings of this study in a broader context, and provides possible explanations for the discrepancy of patterns of axonal excitability changes in acquired and genetic potassium channelopathies.

Introduction

Ion channelopathies are caused by dysfunction of channels due to hereditary or acquired disorders. Channelopathies affect almost all areas of neurological practice, including epilepsy, movement disorders, migraine, peripheral neuropathy, pain syndrome, and myopathy (Kullmann and Waxman, 2010). Over the past 2 decades, the concept of ion channelopathy has been significantly expanded. In addition to genetic channelopathies, neuronal or axonal ion channel function can be altered in a number of conditions, such as acquired (autoantibody-mediated, toxic, and metabolic) and even neurodegenerative (motor neuron disease) or inflammatory diseases (multiple sclerosis, immune-mediated neuropathies) (Krishnan et al., 2009; Kuwabara and Misawa, 2004, 2008).

Furthermore, ionic conductances are largely affected by membrane potential and trans-axonal ionic concentration. For example, in chronic dialysis patients, axons are depolarized by hyperkalemia, resulting in increased axonal sodium and potassium conductances (Kiernan et al., 2002). Conversely under hypokalemia axonal membrane is hyperpolarized, and the ionic conductances are reduced (Kuwabara et al., 2002b). Another example is diabetic neuropathy; under hyperglycemia, the activation of the polyol pathway leads to reduced Na^+/K^+ pump activity, and the resulting intra-axonal sodium accumulation decreases sodium currents due to decreased trans-axonal sodium gradient. In this regard, uremic or diabetic neuropathy is a type of channelopathy (Kitano et al., 2004; Misawa et al., 2006a,b). Therefore ionic conductances and axonal excitability are dependent on the environmental conditions, as well as the channel function itself.

Separately, an exciting development has been the identification of neurological disorders that are associated with specific antibodies to ion channels. The most common CNS syndrome associated with voltage-gated potassium channel (VGKC) antibodies is a form of limbic encephalitis (Irani et al., 2010). Another example of anti-VGKC antibody-associated syndrome is acquired neuromyotonia, also termed as Isaacs syndrome and cramp-fasciculation syndrome, that is characterized by muscle cramp, myokymia, and fasciculations due to spontaneous repetitive firing of motor axons. The motor axonal hyperexcitability is caused by suppression of fast potassium channels by anti-VGKC antibodies (Hart et al., 2002).

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In this issue of *Experimental Neurology*, Park et al. reported changes in peripheral axonal excitability in patients with limbic encephalitis or acquired neuromyotonia, whose sera had high-titer of anti-VGKC antibodies (Park et al., 2014). Axonal excitability testing was performed at the wrist of the median nerve motor axons. Patients with limbic encephalitis demonstrated prominent abnormalities in peripheral axonal excitability during the acute phase, but the pattern of excitability property changes was not consistent with blockade of VGKC, and was possibly explained by reduced sodium currents because most of the patients had hyponatremia due to a syndrome of inappropriate antidiuretic hormone secretion.

They also showed that patients with acquired neuromyotonia demonstrated no significant changes at the site of stimulation. The total findings suggest that serum anti-VGKC antibodies did not affect excitability properties at the site of stimulation (tested site), largely because the antibodies cannot assess the tested motor axons by the blood–nerve barrier (see below). The findings indicate that not only the effects of anti-VGKC antibodies, but also a complex interaction of multiple factors should be taken into consideration in the clinical situation, and therefore this study is interesting and of clinical significance.

Nerve excitability testing

Testing the excitability of axons can provide insights into the ionic mechanisms underlying the pathophysiology of axonal dysfunction in humans. The technique of threshold tracking was developed in the 1990s, to non-invasively measure a number of axonal excitability indices, which depend on membrane potential and on the sodium and potassium conductances. By delivering a conditioning stimulus, which alters membrane potential or activates specific ion channels, the current required to produce a target potential (threshold) will change. The techniques have been extensively applied to the study of the biophysical properties of human peripheral nerves *in vivo* and have provided important insights into axonal ion channel function in health and disease. This commentary focused on assessment of potassium channel function (for the details on methodology and interpretations of nerve excitability testing, please refer to previous excellent review articles [Bostock et al., 1998; Krishnan et al., 2009]).

There are many types of potassium channels on axons (Reid et al., 1999), but it is convenient, for clinical purposes, to restrict discussion to two groups that are dependent on the membrane potential, those with fast kinetics (fast potassium channels) and those with slow kinetics (slow potassium channels). Fast potassium channels are located in the juxta-paranodal region, where they contribute to the resistance of the internodal membrane and limit the depolarizing afterpotential responsible for supernormality. Slow potassium channels have a density at the node 25 times that at the internode, but their kinetics is too slow to allow them to affect the action potential directly. They help to determine the resting membrane potential, contribute to accommodation to depolarizing stimuli, and are responsible for the late subnormality. In excitability testing, the S1d phase of threshold electrotonus and supernormality are limited by fast potassium conductance, and the S2 phase and subnormality are caused by slow potassium conductance. Therefore, patterns of combined findings of the threshold electrotonus and recovery cycle can provide information about fast and slow potassium conductances (Table 1; Fig. 1).

Briefly, in the threshold electrotonus studies, the membrane potential was altered by the use of DC polarizing currents that were 40% of the unconditioned threshold. Depolarizing and hyperpolarizing currents were used, each lasting 100 ms, and their effects on the threshold current for the test motor responses were examined. The recovery cycle of axonal excitability after a single supramaximal stimulus was measured by delivering the test stimulus at different intervals after the conditioning stimulus. The intervals between the conditioning and test stimulation were changed systematically from 2 to 200 ms. When fast potassium channels are blocked, both the S1d phase and supernormality should increase (Bostock et al., 1998).

Table 1
Axonal excitability indices and potassium channel conductance.

Parameter	Ion channel
Threshold electrotonus	
S1d	(Limited by) fast potassium channel
S2	Slow potassium channel
S3	Inward rectifying channel
Recovery cycle	
Refractoriness	Recovery from inactivation of sodium channel
Supernormality	(Limited by) fast potassium channel
Late subnormality	Slow potassium channel

S1d = peak of the slow phase in the depolarizing direction, see Fig. 1.

Genetic potassium channelopathy (episodic ataxia type 1) and excitability

Detailed nerve excitability findings in episodic ataxia type 1, a representative genetic potassium channelopathy, have been reported (Tomlinson et al., 2010); episodic ataxia type 1 is a neuronal channelopathy caused by mutations in the KCNA1 gene encoding the fast potassium channel subunit Kv1.1. The disorder presents with brief episodes of cerebellar dysfunction and persistent neuromyotonia, and is associated with an increased incidence of epilepsy. The S1d phase in threshold electrotunus, and supernormality in the recovery cycle were prominently greater than those in normal controls. The findings exactly show loss of function of fast potassium channels. Using these two parameters, the patients with episodic ataxia type 1 and controls could be clearly separated into two non-overlapping groups. The authors concluded that nerve excitability testing is useful in diagnosis, since it can differentiate patients with episodic ataxia type 1 from normal controls with high sensitivity and specificity.

In a study by Park et al. (2014), the authors presumably expected the same findings, but results of actual recordings with the same techniques in patients with anti-VGKC antibodies were very different from those in patients with episodic ataxia type 1. The S1d phase of threshold electrotonus, and supernormality in the recovery cycle were smaller than those in normal controls, the opposite patterns to those of episodic ataxia type 1 (see Fig. 1 in their paper). The findings indicate that changes in axonal excitability in patients with anti-VGKC antibodies are not caused by potassium channel blocking, and other factors should have contributed to the altered excitability. The unexpected results are considered to be due to multiple factors, and the inaccessibility of the site (at the wrist portion of the median nerve) to the antibodies because of the blood–nerve barrier is one of the factors.

The blood–nerve barrier and autoantibodies

Because of the blood–nerve barrier, large molecule substances such as immunoglobulin (antibodies) cannot access the nerve trunk. The internal microenvironment in the peripheral nerves is highly regulated. In humans, this regulation is facilitated by specialized tight junction-forming endoneurial microvascular endothelial cells. The endoneurial endothelial cells come in direct contact with circulating blood and, thus, can be considered the blood–nerve barrier.

However, the blood–nerve barrier is anatomically deficient in the distal nerve terminals, nerve roots, and dorsal root ganglia (Olsson, 1990). In immune-mediated neuropathies, such as Guillain–Barré syndrome and chronic inflammatory demyelinating neuropathy, it is established that the distal nerve terminals and nerve roots, where the blood–nerve barrier is deficient, are preferentially affected (Brown