Nerve Excitability Studies in the Present Era

Most clinicians with more than a passing interest in peripheral nerve diseases may have come across recent research in the area of axonal excitability. Excitability testing is not, in fact, a particularly new technique but its historical vogue was short-lived because of the development of accurate methods of measuring nerve conduction velocities in the last half century. More recently, it has experienced a renewed interest in specialised laboratories in the UK, Germany, Australia and Japan, because of highly refined software that has enabled rapid and reproducible in vivo testing of subjects.

Excitability testing involves measuring the threshold current required to stimulate an axon or population of axons, most commonly at a single accessible nerve point in the limb. It measures the relative ease with which an axon or axons in a nerve bundle can be depolarised past the threshold for excitation. In this regard, it differs from nerve conduction which is primarily concerned with the speed and security of impulse conduction between two points on the largest and fastest axons. The latter has been particularly useful for the study of demyelinating neuropathies, but even so, conduction velocity can be altered by changes in membrane potential and Na^+ channel permeability, as well as disorders of myelination, not to mention cooling.

The method of excitability testing most commonly employed now uses threshold tracking.[1,2] When determining the threshold of a nerve bundle, one measures the response obtained either from the compound motor action potential amplitude over muscle when stimulating the motor fibres, or the sensory action potential when stimulating cutaneous afferent fibres. The stimulus current is varied to produce a target potential of fixed size. Then, membrane potential is disturbed by subthreshold conditioning currents or by suprathreshold stimuli that cause axons to discharge. The proportional change in current required to elicit the target potential in response to these conditioning stimuli is measured. Such relative changes in threshold are more useful than absolute changes which can be influenced by current access to the nerve.

A battery of excitability tests is most efficiently performed now with software ('QTracs') developed by Professor Hugh Bostock at the Institute of Neurology, London. Multiple measures can be obtained in a short and convenient protocol ('Trond') which is usually more tolerable to the subject than standard nerve conduction studies.[3] The study usually takes 10 minutes for motor, and 15-20 minutes for sensory studies. Most published studies have been performed on the median nerve at the wrist. There are four main domains in the most commonly employed protocol:

(i) strength-duration properties – this is the study of rheobase (the minimum charge required to just cause excitation with a current of infinitely long duration) and chronaxie (the current duration corresponding to twice the rheobase) estimated by different pulse widths and their corresponding intensities required to elicit the target potential;

(ii) threshold electrotonus – often used synonymously with excitability tests. Threshold electrotonus provides insight into how axons accommodate (adapt to) long-lasting changes in membrane potential. In it, we measure the changes in threshold that occur during and after subthreshold depolarising and hyperpolarising currents of set intensity but of varying length;

(iii) current-voltage relationship – here, the threshold change is measured immediately after the injection of subthreshold currents of set length but of varying intensity, in the depolarising and hyperpolarising directions;

(iv) recovery cycle – this documents the threshold changes following a suprathreshold conditioning stimulus that causes the axons to discharge. The recovery cycle consists of three phases: absolute and relative refractory periods, the early superexcitable period and late subexcitable period.

From earlier experimental work on the myelinated rat axon and human studies, the patterns of changes can give an indication of channel permeabilities. The patterns of threshold alterations and their interpretation are too complex for the scope of this article, but some fundamental processes can be deduced with this method. These include a change in the resting membrane potential. The properties of various voltage-gated ion conductances at the node and internode can also be determined, such as the behaviour of transient and persistent Na^+ channels which are responsible for depolarisation during activation, fast and slow K^+ channels which limit depolarisation, and inwardly rectifying currents which permit ingress of Na^+ and K^+ ions and limit activity-dependent hyperpolarisation. The interpretation of the changes is now greatly aided by a computer model developed by Professor Bostock, which can alter conductances and weightings of different parameters both at the node and internode, to see if the changes observed in testing can be simulated in the model.[4] A noteworthy example is the faithful reproduction of the test results in a group of patients suffering acute tetrodotoxin poisoning by reducing Na^+ channel permeability in the model by a factor of 2.[5] Tetrodotoxin is the poison of puffer fish and blocks Na^+ channels.

The table lists the findings of burgeoning clinical research that has now been performed in various neuropathic disorders over the years. The method is also proving of worth in assessing plastic changes seen in peripheral nerves following central nervous lesions and disorders.[6] It can be modified to assess the effect of a physiological experiment such as limb ischaemia (see Figure) on a single excitability parameter. No doubt, the list will expand with the increasing availability of commercial software and hardware systems developed for the method above. There are though, limitations to this elegant method for studying nerve pathophysiology. First of all, there has to be a sufficiently large target response to study, and this can be a problem with moderate to severe neuropathies. Testing is restricted to sites of nerve accessibility, which may explain the lack of evidence for hyperexcitability in some conditions such as neuromyotonia, where the ectopic motor discharge may arise from nerve terminals.[7]

What relevance does this have presently for the clinician at the coalface not involved in studying nerve physiology? To date, the technique has not proved a useful diagnostic tool. Even where very significant differences have been observed between patient and control groups in a certain disorder, the variability of the results has prevented unambiguous categorisation of a single test result in a patient. Further, there has not been shown to be sufficient specificity in the various disorders, with sometimes different conditions producing similar alterations in their excitability profiles. For example, the changes observed in end-stage liver disease are quite similar to those of Fabry disease, showing perhaps the result of a common final pathway of ischaemic deactivation of the Na^+/K^+ ATPase pump.[8,9] However, there could be a role for monitoring nerve function. Another problem is that the properties assessed belong to nerves that are still able to generate

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Figure

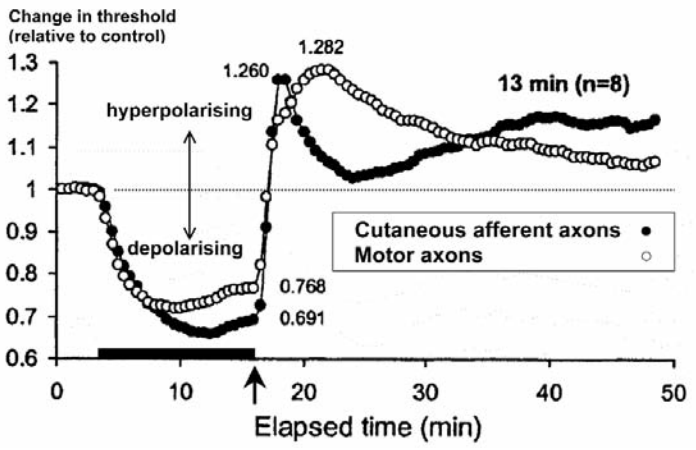

Figure legend:
Median cutaneous afferent and motor axons stimulated at the wrist. Mean excitability data for 8 subjects, before, during (heavy bar) and after ischaemia for 13 min with a cuff around the upper arm. During ischaemia, there is a decrease in threshold (depolarisation) and, following release of ischaemia at the vertical arrow, there is an increase in threshold (hyperpolarisation) relative to the control level. Note that the changes for sensory and motor axons differ. The subjects all experienced post-ischaemic paraesthesiae following release of the ischaemia, and they occurred during the falling phase of the notch on the threshold trace for cutaneous afferent axons. None developed post-ischaemic fasciculation.

impulses. Paradoxically, if the nerves with the most disordered thresholds for excitation drop out, excitability studies might normalise. However, nerve excitability studies can provide unique information about the state of the axon and, as such, they complement other neurophysiological tests: standard nerve conduction, EMG and motor unit estimation. Excitability studies have not only advanced our understanding of nerve dysfunction but also led to new approaches to management. For example, one study in Machado-Joseph disease (SCA-3) detected increased strength-duration time constant, probably due to an excessive persistent Na^+ current. The authors were prompted to try mexiletine to reduce these currents, and this resulted in a partial normalisation of the abnormality and a dramatic reduction in disabling muscle cramp in their cohort.[10]

For a more comprehensive review of the topic, the reader is referred to The Handbook of Clinical Neurophysiology, Elsevier, with the chapter "Assessment of Nerve Excitability Properties in Peripheral Nerve Disease" by Lin, Kiernan, Burke and Bostock.

Table: Clinical peripheral nerve excitability studies to date

Disorder	*Reference (first author)*
Metabolic and medical conditions	
Diabetic neuropathy	*Weigl 1989, Strupp 1990, Horn 1996, Kuwabara 2002, Kiernan 2002, Kitano 2004, Krishnan 2005, Misawa 2005/6, Yerdelen 2007*
Uraemic neuropathy	*Kiernan 2002, Krishnan 2005/6*
Hepatic neuropathy	*Ng 2007*
Critical illness neuropathy	*Z'Graggen 2006*
Fabry disease	*Tan 2005*
Acquired hypokalaemic paralysis	*Kuwabara 2002*
Mononeuropathies	
Carpal tunnel syndrome	*Mogyoros 1997, Kiernan 1999, Cappelen-Smith 2003*
Hemifacial spasm	*Kiernan 2007*
Motor neuropathies	
Amyotrophic lateral sclerosis	*Bostock 1995, Horn 1996, Mogyoros 1998, Priori 2002, Nakata 2006, Kanai 2006, Vucic 2006/7*
Multifocal motor neuropathy	*Kaji 2000, Kiernan 2002, Cappelen-Smith 2000/2*
Acquired neuromyotonia	*Maddison 1999, Kiernan 2002*
Acquired and hereditary demyelinating neuropathies	
CIDP	*Cappelen-Smith 2000/1/2*
AIDP	*Kuwabara 2002, Sung 2003*
Charcot-Marie-Tooth 1a	*Nodera 2003*
Chemotherapy and toxins	
Taxol-cisplatin-oxaliplatin	*Quasthoff 1995, Hanauske 1995, Schilling 1997, Krishnan 2006*
Tetrodotoxin poisoning	*Kiernan 2005*
Central nervous system disorders	
Cerebral stroke	*Jankelowitz 2007*
**GEFS⁺*	*Kiernan 2005*
Spinal cord injury	*Lin 2007*
Other	
Machado-Joseph disease	*Kanai 2003*
Myotonic dystrophy	*Krishnan 2006*
**GEFS⁺ = Generalised epilepsy with febrile seizures plus*	

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