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Axonal Excitability and Intermittent Conduction Block in Demyelinated Axons / *Demiyelinize Aksonlarda Aksonal Uyarılabilirlik ve Aralıklı İletim Bloğu*

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ABSTRACT

Healthy myelinated axons conduct securely because of a high density of Na^+ channels at the node of Ranvier, but conduction in demyelinated axons is precarious. Conduction block occurs when the driving current at the blocking node is insufficient to reach threshold for action potential generation. Conduction block can be stable, detectable by routine nerve conduction studies with supramaximal stimuli delivered at 1 Hz, or intermittent, due to either hyperpolarization at the blocking node or a reduction in the driving Na+ current (or both). There are a number of physiological mechanisms that will cause partially demyelinated axons to stop conducting, e.g., changes in membrane potential (both depolarizing and hyperpolarizing), ischaemia and its release, and fluctuations in temperature. As a result, a patient's deficit will fluctuate if a sufficient number of axons start or stop conducting. The detection of intermittent conduction block requires protocols additional to the routine test with supramaximal stimuli at 1 Hz to a motor nerve of a resting patient. A protocol that should detect intermittent conduction block as well as stable conduction block is presented.

Key words: *conduction block, demyelination, axonal excitability, membrane potential, threshold tracking, safety margin*

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ÖZET

Demiyelinize Aksonlarda Aksonal Uyarılabilirlik ve Aralıklı İletim Bloğu

Sağlıklı miyelinize aksonlar, Ranvier düğümündeki Na^+ kanallarının büyük yoğunluğu nedeniyle sağlıklı bir iletim sağlar, ama demiyelinize aksonlardaki iletim istikrarsızdır. Bloke eden düğümdeki işletim akımı aksiyon potansiyeli oluşturma eşiğine ulaşmada yetersiz olduğunda iletim bloğu ortaya çıkar. İletim bloğu stabil olabilir, 1 Hz'de verilen supramaksimal uyaranlarla yapılan rutin sinir iletimi çalışmalarında saptanabilir ya da, ya bloke eden düğümdeki hiperpolarizasyona ya da işletim sağlayan Na^+ akımındaki bir azalmaya (ya da her ikisine) bağlı olarak aralıklı olabilir. Parsiyal demiyelinize aksonların iletiminin durmasına neden olan, örn., membran potansiyelindeki değişimler (hem depolarize eden hem de hiperpolarize eden), iskemi ve iskeminin düzelmesi ve ısıdaki dalgalanmalar gibi, bir dizi fizyolojik mekanizma mevcuttur. Sonuç olarak, yeterli miktarda akson

Anahtar Kelimeler: iletim bloğu, demiyelinizasyon, aksonal uyarılabilirlik, membran potansiyeli, eşik izleme, güvenirlik sınırı

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iletime başlar ya da iletimi durdurursa, hastanın eksik iletiminde bir dalgalanma olacaktır. Aralıklı iletim bloğunun saptanması, istirahat halindeki bir hastanın motor sinirine 1 Hz'de uygulanan supramaksimal uyaranlarla rutin teste ek protokoller gerektirir. Stabil iletim bloğunun yanı sıra intermitan iletim bloğunu da saptayacak bir protokol sunulmaktadır.

Routine nerve conduction studies and nerve function

Nerve Conduction Studies have served clinicians well since motor studies became a routine component of the assessment of peripheral nerve function some 50 years ago. However, there are disadvantages in these studies – e.g., they assess only the fastest axons in the nerve, and they rely on supramaximal stimuli, which displace the site of stimulation a few millimeters from the site of the stimulating electrode and may inadvertently activate adjacent nerves in addition to the nerve being tested. Supramaximal stimuli are necessary to ensure that all axons are activated and that the recorded volleys are then maximal despite differences in their excitability or in their proximity to the stimulating electrodes. However, in doing so, such stimuli eliminate any insight into axonal excitability.

When assessing the response to nerve stimulation, it is usual to measure (i) the amplitude and/or area of a compound nerve or muscle action potential, and (ii) the latency or conduction velocity of the fastest axons. The former measures are very variable in repeat studies on the same subjects and in studies on different subjects. However they represent a critical measurement in nerve conduction studies, because they depend on the number of conducting axons. The latter measurements are highly accurate but, paradoxically, conduction velocity is of little importance for symptoms, and conduction abnormalities are asymptomatic if a sufficient number of axons are conducting. There is a tendency to attribute slowing to "demyelination", and criteria have been developed to increase the certainty of this attribution, but slowing can be caused by many factors other than demyelination.

Conduction slowing can be due to many factors, morphological and functional. Morphological changes in the axon that can cause conduction slowing include axonal tapering, axonal attenuation at sites of constriction, axonal regrowth, demyelination, nodal displacement and intussusception, and remyelination with short internodes. Conduction slowing can also be due to changes in the functional status of the axon due to, e.g., inactivation or blockage of Na^+ channels, axonal hyperpolarization, axonal depolarization, and cooling.

While nerve conduction studies are valuable, they tell the clinician little about how peripheral nerves function under natural conditions and, of necessity, there is often little correlation with a patient's symptoms. At times this is good, because conduction slowing in large myelinated axons may be symptomless, but allows nerve pathology to be identified and localised. On the other hand, as a test of nerve function, such studies are limited. Two techniques provide greater insight into how nerves normally function: microneurography, in which an insulated tungsten microelectrode is inserted directly through the skin into a peripheral nerve fascicle to record the natural impulse traffic in human axons under normal or near-normal conditions,[1,2] and nerve excitability testing.[3,4,5] The latter is addressed below.

Nerve excitability

Recently, reliable techniques have been developed to measure the excitability of axons.[3] The techniques rely on submaximal stimuli and, in the most useful and widely accepted technique, "threshold tracking", the intensity of the stimulus is altered by computer to keep the size of the test potential constant, whether that potential is a compound muscle action potential (CMAP) or a compound sensory nerve action potential (CSAP). The critical measurement is the strength of the stimulus current required to produce the target submaximal compound potential, usually 40-50% of maximum, a size chosen by the program to be on the steeply rising

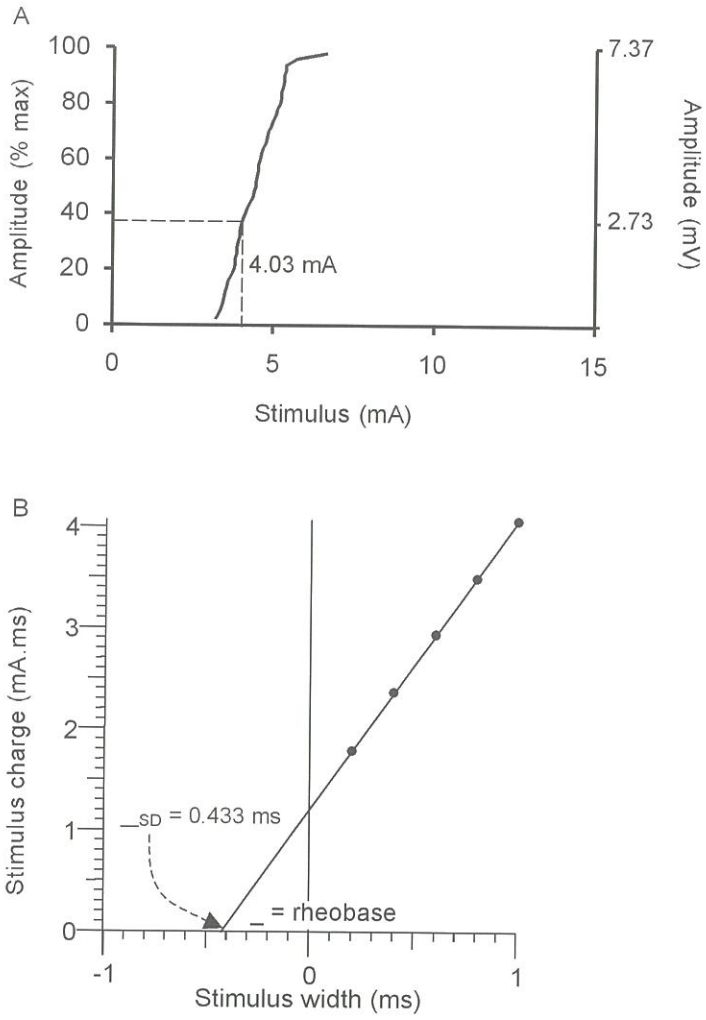

Figure 1. Responses to unconditional stimuli, varying stimulus intensity (A) and stimulus duration (B). A, The stimulus-response curve for thenar motor axons. Note that the curve is quite steep. When there is demyelinating pathology at the stimulus site (e.g., in CIDP) the curve is shifted to the right and is much less steep. The threshold for the target CMAP is the current required to produce the target potential (here 2.73 mV, requiring a stimulus of 4.03 mA). When the demyelinating lesion is proximal (e.g., in MMN with proximal foci), there is no change in this relationship. B, Charge-duration plot for thenar motor axons. When the width of the test stimulus was increased, the stimulus current (in mA) necessary to produce the test CMAP decreased (in a hyperbolic fashion), but the energy in the stimulus (i.e., the stimulus "charge", measured as mA x ms) increased in a linear relationship with stimulus duration. The slope of the relationship equates to the rheobasic stimulus for the test potential. The intercept on duration axis is the chronaxie (also called the strength-duration time constant, ±SD).

phase of the stimulus-response curve for both the CMAP and the CSAP (Fig. 1A, where the target CMAP was 37% of maximum). This stimulus current (4.03 mA in Fig. 1A) is referred to as the "threshold" for the target potential. Changes in excitability of axons produce changes in the current required to produce a compound potential of the target size. Using a computer running the program Qtrac (©Professor Hugh Bostock, Institute of Neurology, University College, London), the stimulus intensity is altered if the recorded potential deviates significantly from the target amplitude, in a procedure termed "threshold tracking".

The absolute value of the stimulus current is affected by the impedance of skin and other tissue factors and the proximity of the nerve to the stimulating electrodes, and is therefore of limited value. However, if a test stimulus is preceded by a suprathreshold conditioning stimulus, there will be a sequence of changes in axonal excitability known as the "recovery cycle", as the excitability of axons that discharged to the conditioning stimulus recover to their control level (Fig. 2). The stimulated axons will pass through phases of refractoriness (causing an increase in threshold that decays over ~3 ms), supernormality (during which axons are more excitable, with a peak at ~6 ms) and late subnormality (during which axons are less excitable, peaking at 30-40 ms) before finally returning to

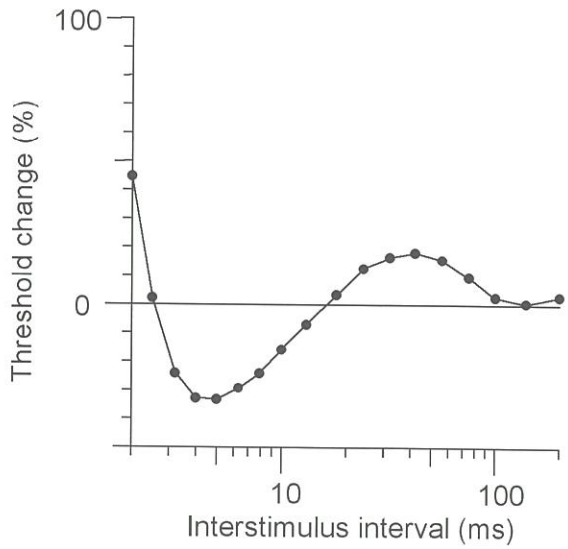

Figure 2. Changing excitability using a suprathreshold conditioning stimulus. The recovery cycle represents the time course of the changes in excitability of axons as they recover following a conditioning discharge. The excitability of thenar motor axons was measured as the change in current required to produce a test CMAP that was 37% of maximum, and was determined for conditioning-test intervals of 2 ms to 200 ms. Axons were refractory at short intervals, supernormal at intervals from 3-15 ms and then subnormal.

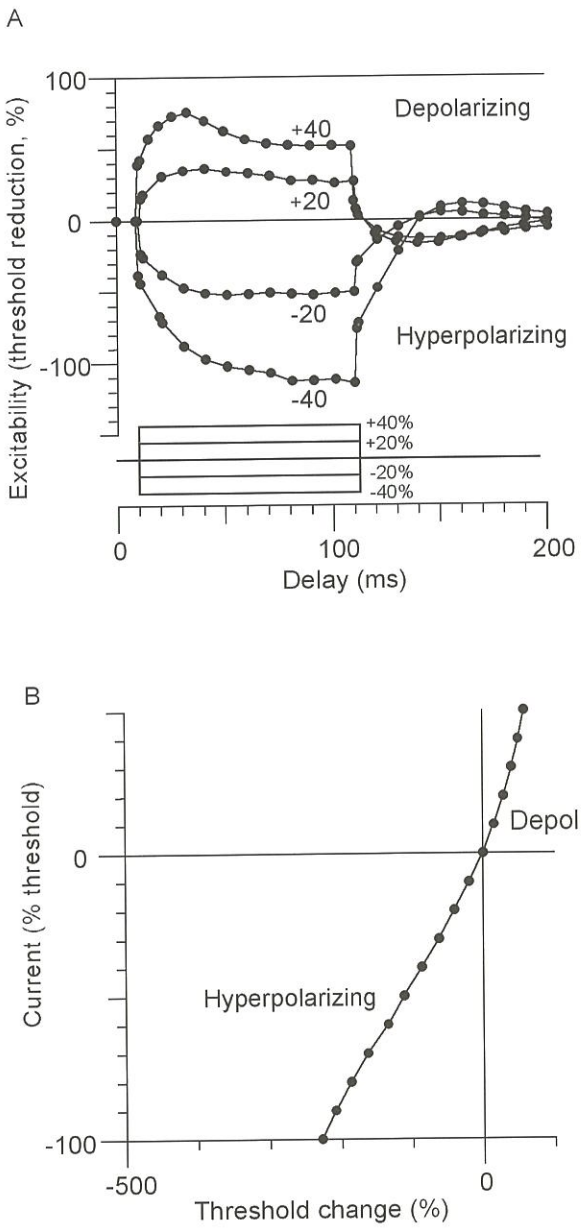

Figure 3. Changing excitability using subthreshold conditioning stimuli. A, Threshold electrotonus. The changes in excitability of thenar motor axons during and after subthreshold square-wave currents lasting 100 ms. The square waves below the data plots represent the applied polarizing currents: depolarizing, set at 20% and 40% of the threshold for the test potential (plotted upwards) and hyperpolarizing, set at -20% and -40% of the threshold for the test potential (plotted downwards). Notice that the axonal response to the square-wave current is not a square wave because voltage-dependent ion channels at the node and on the internode cause accommodation. See Bostock et al. (1998) for further details. B, The current-threshold relationship for thenar motor axons. The stimulus current required to produce a test CMAP 37% of maximum was measured at the end of a 200-ms long subthreshold square-wave current, the strength of which was changed in 10% steps from +50% (depolarizing, top right) to -100% (hyperpolarizing, bottom left). The curve illustrates accommodation to depolarizing currents by the tendency to become vertical (upper right) due to activation of K^+ conductances, and accommodation to hyperpolarizing current (by the extent to which the lower part of the curve approaches vertical) due to activation of conductances producing "inward rectification".

control level at ~100 ms.[6] Alternatively, the test stimulus can be delivered before, during and after a long (100 ms) subthreshold square-wave conditioning stimuli that depolarize or hyperpolarize the nerve, in a procedure known as "threshold electrotonus" (Fig. 3A; see Bostock et al., 1998, ref. 3) or the test stimulus can be delivered at the end of a long (200 ms) polarizing current, the intensity of which is altered in steps from 50% depolarizing to 100% hyperpolarizing, thus producing a current-threshold relationship analogous to the conventional current-voltage relationship (Fig. 3B, see Kiernan et al., 2000b, ref. 4). In addition, stimulus-response curves can be constructed (Fig. 1A), and if the duration of the test stimulus is varied the strength-duration properties (Fig. 1B) of the axons can be calculated.[7]

Under most circumstances, axonal excitability accurately reflects membrane potential but, as noted above, threshold is not a direct measure of membrane potential. In addition, excitability can deviate from membrane potential under two well-documented circumstances – ischaemia (due to inactivation and blockage of Na^+ channels, see Lin et al., 2002, ref. 8) and during hyperventilation (which alters surface charge but has little effect on membrane potential, see Mogyoros et al., 1997, ref. 9).

Membrane potential

The above measures of axonal excitability are sensitive to membrane potential, and will change appropriately when axons are depolarized or hyperpolarized. For example, a depolarizing change in membrane potential will:

(i) shift the stimulus-response curve to the left, so that less current is required to activate the axons (i.e., it will decrease the "threshold" for a submaximal test potential that is 40% of maximum),
(ii) increase the degree of refractoriness measured 2 ms after a suprathreshold conditioning stimulus and increase the duration of the relative refractory period (changes that are due to depolarization-induced

inactivation of Na^+ channels),
(iii) decrease the degree of supernormality measured at a conditioning-test interval of 6 or 7 ms (due to depolarization-induced opening of fast K^+ channels on the paranodal membrane),
(iv) increase strength-duration time constant, tSD (because of activation of persistent Na^+ channels, i.e., Na^+ channels that inactivate very slowly if at all), and
(v) alter the pattern of threshold electrotonus and change the current-threshold relationship.[3,10]

Examples of normal data for each of these measures are shown in Figs. 1-3. A difference in membrane potential should result in coherent changes in these indices, and a conclusion that there was a change in membrane potential would be more convincing if multiple indices were measured. Bostock and colleagues have now developed and validated rapid testing protocols for motor axons[4,10] and sensory axons,[11] and a "Windows" version of the Qtrac program has been written. Many studies have now been undertaken in patients (Table 1; see also Lin et al., 2005 where references and further details are given, ref. 5). When a commercial computer-controlled constant-current source becomes available, these studies will be available to clinicians as a potentially useful addition to routine nerve conduction studies.

Table 1. Studies of axonal excitability in neuropathic disorders

- diabetic polyneuropathy
  - smaller ischaemic changes in threshold
  - decreased inward rectification (I_H)
- uraemic neuropathy
  - axonal depolarization reversed by dialysis
- chronic demyelinating polyneuropathies [e.g. CIDP]
  - activity-dependent block
  - stimulus/response curves shifted to right; low τ_{SD}
- acute demyelinating polyneuropathies [AIDP, AMAN]
- toxic neuropathies [taxol/cisplatin]
  - collapse of threshold electrotonus - ? leaky axon membrane
- ALS/MND
  - abnormal threshold electrotonus – ? decreased K^+ currents
  - increased τ_{SD} – ? increased I_{NaP}
- mononeuropathies [CTS]
  - high rheobase
- acquired neuromyotonia
  - increased τ_{SD} – controversial
- Machado-Joseph disease
  - increased τ_{SD}
  - responsive to Mexilitine
- acute hypokalaemia
  - axonal hyperpolarization
- acute puffer-fish poisoning (poisoning by tetrodotoxin, a potent blocker of Na^+ channels)
- GEFS+ (Generalized Epilepsy with Febrile Seizures +), with defined mutations of Na^+ channels

For references, see Lin et al. (2005), ref. 5

Manoeuvres that can change membrane potential

As mentioned above, threshold usually reflects membrane potential but does not quantify it. However, further insight can come from disturbing membrane potential. This can be done by studying the excitability changes following a single discharge or those produced by subthreshold currents (see above). It can also be useful to use manoeuvres to change membrane potential. The two most studied manoeuvres are:

(i) Maintained activity. Clinically it is easier to study motor axons, using a maximal voluntary contraction, usually for 1 min, to produce a prolonged high-frequency discharge of the axons. The exact discharge rate is not known and will vary for different axons, but in practice this matters little provided that effort is truly maximal (and the patients do not have an upper motor neurone lesion that prevents them from fully activating the motor neurone pool). Sensory axons can be studied, using electrical stimulation at supramaximal levels to produce a prolonged high-frequency discharge, but not all patients tolerate such stimulation.
(ii) Ischaemia for 10 min and its release. The effects of ischaemia on sensory and motor axons can be tracked quite easily. The post-ischaemic changes in threshold may take up to one hour to return to the control level. Interestingly, repeating the ischaemic episode soon after threshold has recovered to the pre-ischaemic level produces a less prominent response, indicating that the manoeuvre may have long-lasting effects on the axon, effects that these tests do not easily detect. This underlies the recommendation in Table 2 that tests of the effects of ischaemia and voluntary contraction on impulse conduction should be undertaken on different days.

Table 2. Testing for conduction block

- Ensure that the limb is warm (skin temperature >32°C)
- Use supramaximal stimuli
  – if only one, ensure that it is >40% supramaximal
  – if two, set the second 20% higher than the first and alternate between the two stimuli and ensure that they produce identical CMAPs
- Deliver the supramaximal stimulus (or alternate the 2 stimuli) at 1/sec before and after maximal voluntary contraction of the test muscle for 1 min
- In a separate test session, deliver stimuli at 1/sec before, during and after ischaemia of the limb for 10 min (this should be on a separate day from the MVC because the changes in excitability can be long-lasting)
- If the results are not consistent with expectation, repeat them after warming.

When an axon conducts a train of impulses, intracellular Na^+ concentration increases, and the electrogenic Na^+/K^+ pump is activated to restore the ionic balance across the axonal membrane (Fig. 4). The pump extrudes 3 Na^+ ions in exchange for 2 K^+ ions, and the resulting electrical imbalance hyperpolarizes the axon. The degree of hyperpolarization of motor axons in the median nerve at the wrist after a maximal voluntary contraction of the thenar muscles for 1 min is ~40%, and threshold does not return to control levels for some 10-15 min.[12] If the duration of the contraction is briefer, the degree of hyperpolarization is less and it recovers more quickly but, even after contractions for only 15 s, threshold may increase by 15-20%. A 40% hyperpolarization will not jeopardise conduction in normal axons because the safety margin for action potential generation at the node of Ranvier is normally 5:1 (i.e., 5 times as much current is produced as is required to reach threshold). However, as addressed below, in axons that are only just managing to conduct, this degree of hyperpolarization can precipitate conduction block.[13,14]

Ischaemia and its release also produce changes in membrane potential (Fig. 5). During ischaemia, paralysis of the pump (which is energy-dependent and normally contributes ~15 mV to resting membrane potential) results in increases in extracellular [K^+] and in intracellular [Na^+]. The pump is normally active at rest and has a hyperpolarizing influence on axons, and its paralysis by ischaemia therefore results in depolarization. The depolarization will inactivate Na^+ channels and, in addition, ischaemic metabolites may block Na^+ channels.[8] Both of these effects will decrease the driving current at involved nodes. As discussed below, if the size of the action current is critical, a reduction in the number of functioning channels can offset the increase in excitability and precipitate conduction block.[15]

With the release of ischaemia, axons hyperpolarize as pump activity is restored and it strives to restore Na^+ balance across the axonal membrane (Fig. 5). The extent of hyperpolarization may be 20-30%, gradually decaying over 20-30 min, again insufficient to produce conduction block in healthy axons, but capable of doing so when the safety margin is sufficiently impaired.[15]

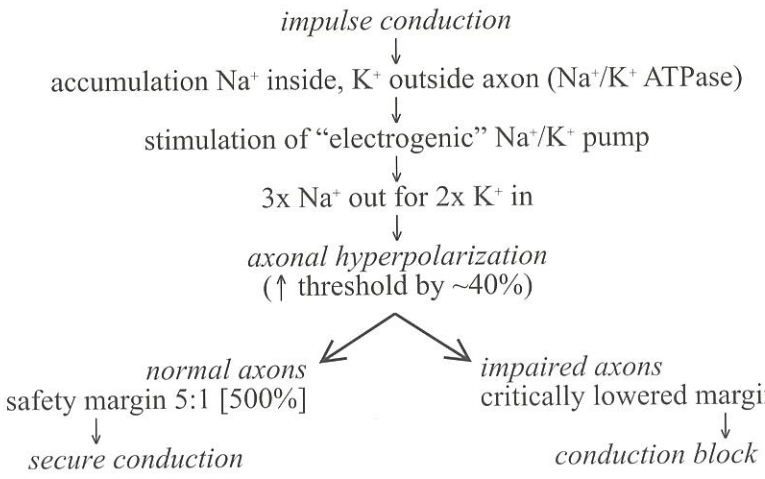

Figure 4. Activity dependent hyperpolarization.

Intermittent conduction block

Healthy axons conduct securely because the high density of Na^+ channels at the node of Ranvier provides a large action current that is ~5 times greater than is required to reach threshold (i.e., they have a high safety margin for action potential generation, ~5:1). Conduction in demyelinated axons is precarious because at pathological nodes the driving current is reduced and may not reach or may only just reach threshold for the action potential.[16] An axon will fail to conduct when the driving current at any node along the axon fails to generate an action potential. In demyelinating diseases, pathology is not uniform across involved axons: in some axons, the demyelination may render the axon completely unable to conduct (very low safety margin, perhaps <0.8:1), in some the driving current may only just fail to reach threshold (>0.9:1), in some the driving current may reach threshold but only just (1.1:1), and in some axons impulse generation will be reasonably secure despite a moderately impaired safety margin (2:1).

As mentioned above, conduction block can occur as a result of the axonal hyperpolarization that is the result of the affected axons conducting impulses, and this is refered to as activity-dependent conduction block (Fig. 4). Activity can increase threshold by ~40%, insufficient to cause conduction block in healthy axons, but sufficient to impair action potential generation in some axons in Multifocal Motor Neuropathy (MMN; Kaji et al., 2000, ref. 13) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP; Cappelen-Smith et al., 2000, ref. 14), in which the safety margin for generating an action potential is severely reduced. The block lasts only as long as the axons are sufficiently hyperpolarized, i.e., perhaps a few minutes. They recover with rest until they again become active. This phenomenon can account for fatigue and fading of strength in demyelinating diseases (e.g., MMN, CIDP and multiple sclerosis). In addition, when ischaemia is released, axons undergo post-ischaemic hyperpolarization (Fig. 5), which can increase threshold by ~20%, and accentuate conduction block in CIDP.[15] The relationship between the degree of block and the increase in threshold is the same with post-ischaemic conduction block as with activity-dependent conduction block, and this implies that the same phenomenon, i.e., the hyperpolarizing change in membrane potential, is probably responsible for the block with the two manoeuvres.

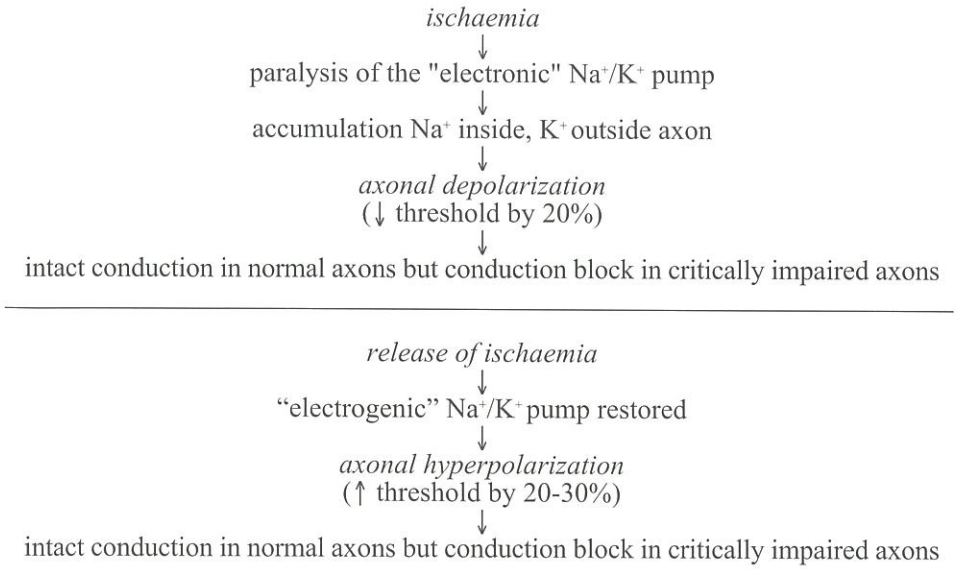

Figure 5. Effects of ischemia and its release.

Conduction block can also occur if there is a further reduction in the driving Na^+ current at the node of Ranvier when conduction is already precarious. This occurs because a maximal Na^+ current is required if the safety margin for action potential generation is low.

Temperature-induced changes in the Na^+ current can produce conduction block in demyelinated axons: a higher temperature speeds up Na^+ channel kinetics, decreases the time integral of the Na^+ current and thereby reduces the driving current for the action potential. [In MMN "cold paralysis" is well documented, a paradox for a supposedly demyelinating disorder, but one that may have been resolved by Kiernan et al., 2002, ref. 17].

Alternatively, reduced availability of functioning Na^+ channels can occur if there is blockade of Na^+ channels by, e.g., local anaesthetics, ischaemic metabolites, puffer fish poisoning (which is due to tetrodotoxin, TTX), or if there is inactivation of Na+ channels. As mentioned above, inactivation of Na+ channels and their blockade by ischaemic metabolites occur during ischaemic depolarization, and together they can accentuate conduction block in some patients with CIDP (Fig. 5). Presumably the increased excitability of axons due to ischaemic depolarization is insufficient to offset the decreased availability of Na^+ channels due to inactivation.

CONCLUSIONS

In demyelinating diseases, the deficit experienced by patients is due to the combined effects of (i) axonal loss and (ii) conduction block. The latter may be stable conduction block or be manifest only intermittently – though usually the intermittent inability of some axons to conduct impulses accompanies a relatively stable inability of other axons to conduct impulses, because the involvement of axons by the pathology is not uniform. If axons are partially demyelinated but still conducting, they are susceptible to conduction failure, and routine nerve conduction studies will not detect the full extent of the deficit that the patient experiences. A better correlation of diagnostic testing with the deficit that the patient experiences would occur if the testing procedure could detect the intermittent conduction block that can be associated with changes in axonal excitability. As discussed above, fluctuations in the ability of axons to conduct impulses can be due to changes in membrane potential of axons that have a reduced safety margin for action potential generation, or to further changes in the Na^+ current driving the action potential. Depolarization can reduce the number of Na^+ channels available at the node so that the driving current no longer reaches threshold, even though depolarization itself moves membrane potential closer to threshold. Stimuli given at 1 Hz to a resting patient may not detect intermittent conduction failure in partially demyelinated axons due to changes in membrane potential or to changes in the driving Na^+ current, but the protocol in Table 2 should do so.

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