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Technical note

Calculation of extracellular potentials produced by an inclined muscle fibre at a rectangular plate electrode[1]

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Abstract

Generally the anatomy of muscles is rather complex, and the fibres have various inclination angles within the muscles. We suggest a fast and reliable way to calculate extracellular potentials produced at a point or rectangular plate electrode by a muscle fibre of finite length with an arbitrary inclination. A muscle fibre was considered to be a linear timeshift-invariant system of potential generation. Then, similar to the fibre without inclination, the extracellular potential produced by an inclined fibre was represented as the output signal of the system; it was calculated as the convolution of the input signal and impulse response. Irrespective of the inclination, the input signal of the system was the first temporal derivative of the intracellular action potential. The impulse response of the system differed for the fibres with inclination. This required a new method of analytical integration over the rectangular electrode area. The approach provides a chance to simulate and analyze motor unit potentials or F-, H- or M-responses produced by muscles of complicated anatomy (circum-pennate or complex pennate type) at electrodes of actual size and location in normals and patients with neuro-muscular disorders. © 1999 IPEM. Published by Elsevier Science Ltd. All rights reserved.

Keywords: Inclined skeletal muscle fibre; Extracellular potentials; Computer modelling; Rectangular plate electrode; Fast calculation

1. Introduction

The majority of muscles consist of fibres with various inclination angles to the skin. Their anatomy can be rather complex: from uni-, bi-, multi-pinnate to circum-pennate or complex pennate type [1,2]. This creates uncertainty in electrode placement and problems with analysis of the detected potentials and their changes [3,4]. The problems increase even more if the electrodes are not point. Complexity of the muscles restricts experimental studies to a number of muscles whose fibres can be considered to be parallel to one another and to the skin surface. An adequate potential simulation could help in understanding the potentials recorded from complex muscles.

Mathematical models of extracellular potentials produced by skeletal muscle fibres usually imply straight fibres without inclination. Few attempts have been made to calculate potentials produced by curved nerve and muscle fibres of finite length [5] or by curved infinite nerve fibres in bounded volume conductors [6]. Both methods were for potentials detected by a point electrode. The aim of this study is to develop a method of making fast and precise calculations of potentials produced at a point or rectangular plate electrode by a finite length muscle fibre with arbitrary inclination. This could be the basis for the calculation of potentials produced by motor units and muscles with a complicated anatomy.

We based our study on a precise and fast way to calculate extracellular potentials produced by muscle fibres and motor units, detected by a rectangular plate electrode, one pair of whose edges was parallel to the fibre course [7]. The solution for a single fibre took into account: finite length of skeletal muscle fibres; the presence of two waves of excitation propagating from the end-plate to the fibre ends; intracellular action potential (IAP) of actual shape; infinite (or semi-infinite) anisotropic volume conductors.

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Calculation of spatially filtered signals produced by a motor unit comprising muscle fibres with non-uniform propagation

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Abstract—*Simulation of actual muscle potentials is necessary to understand processes that underlie changes in electromyographic signals. The work reported aims to analyse existing methods and suggest new ways of calculating precisely the signals (MUS) detected by a multielectrode from motor units (MUs) consisting of homogeneous or inhomogeneous (functionally and geometrically) fibres. Simulation (based on cable equations) of intracellular action potential (IAP) in a muscle fibre with a moderate geometrical inhomogeneity demonstrates that considerable changes in propagation velocity (more than 3.5 times) are accompanied by insignificant changes in the IAP amplitude (< 5%) and IAP shape in the temporal domain. MUS can therefore be considered as the output signal of a timeshift-invariant system whose input signal is the first temporal derivative of the IAP. As a result, calculation of MUS is reduced to a single convolution in the case of muscle composed of both homogeneous and inhomogeneous fibres. The suggested approach is valid for simulation of recordings obtained with points or rectangular plates leading off surfaces from muscles consisting of fibres that are parallel or inclined to the skin surface. The MUS terminal phases are prolonged because of fibre inhomogeneities. The presence of geometrical inhomogeneities results in additional positive–negative phases in MUS.*

Keywords—*Motor unit potential, Single convolution model, Non-uniform propagation, Multielectrode detection, Parallel or inclined muscle fibres*

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1 Introduction

THE ROLE of electromyography is becoming increasingly important in controlling the results of the treatment of neuromuscular diseases and rehabilitation. To understand processes that underlie electromyogram changes, simulation of actual muscle potentials is required. Models of muscle potential should reflect the transmembrane sources which are due to the presence of two waves of excitation (that originate at the end-plate and propagate to the ends of every fibre), geometrical relations between recording electrodes and active fibres, as well as volume conductor properties. A simplified simulation of the transmembrane sources through one or two dipoles (GEORGE, 1970; FUGLEVAND *et al.*, 1992) or tripoles (ROSENFALCK, 1969), gives way to analytical presentation of actual shapes of the intracellular actual potential (IAP) (ROSENFALCK, 1969; TRAYANOVA and DIMITROV, 1982; NANDEDKAR *et al.*, 1985; GOOTZEN, 1990; LATEVA *et al.*, 1996; DIMITROV and DIMITROVA, 1998; DUCHENE and HOGREL, 2000; DIMITROVA *et al.*, 1999). Muscle fibres are usually assumed to be parallel to the skin surface (FUGLEVAND *et al.*, 1992; GOOTZEN, 1990; LATEVA *et al.*, 1996; DIMITROV and DIMITROVA, 1998; MERLETTI *et al.*, 1999; DUCHENE and HOGREL, 2000) and sometimes to be inclined to it (DIMITROVA *et al.*, 1999) or curved (DIMITROV and DIMITROVA, 1980). The volume conductor is considered to be homogeneous and infinite, or sometimes bounded (cylindrical) and inhomogeneous (GOOTZEN, 1990).

The boundaries of a volume conductor are not exactly cylindrical. There is a large veriety of configurations of actual volume conductors and the parameters of inhomogeneties of the volume conductor are usually unknown. When the boundary can be considered as a flat one, the signals (detected by surface electrodes) are double those in an infinite volume conductor. Also, the effect of cylindrical boundaries can be less pronounced than that of finite fibre length (GOOTZEN, 1990). That is why, in the present study, we consider the case of an infinite volume conductor and focus attention on the effects of anatomical and functional parameters of motor units (MUs).

If muscle fibres are homogeneous cylinders, the shape of the IAP as a function of time is considered to be identical in all fibre points and the propagation velocity to be constant along the fibre path. Then the extracellular potentials produced by a single muscle fibre (SMFP) can be expressed through convolution in

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Factors affecting the turns analysis of the interference EMG signal

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Abstract

This study was performed to evaluate the relative significance of changes typical for muscle fatigue on quantitative parameters obtained from turns analysis of simulated intramuscular and surface interference electromyographic (EMG) signals. Effects of reduction of firing rate of motor units (MUs) and changes of intracellular action potential (IAP) profile along active fibers were analyzed. A new analytic function was proposed to simulate changes in IAP shape at different stages of muscle fatigue. In intramuscular EMG, both the decrease in firing rate of MUs and the changes in IAP profile led to reduction in the number of turns per second (NTs) and mean turn amplitude (MTA). The development of fatigue and especially the changes in IAP profile could explain why NTs increased up to only about 50% of maximal voluntary contraction, and remained unchanged above that level of efforts or even decreased. These effects should be especially pronounced in patients with myopathy whose IAP and muscle fatigability are expected to be abnormal. In surface EMG, the MTA increased considerably with fatigue; the sensitivity of NTs to reduction in firing rate (or number of discharges) was low. Thus, the benefits of the turns analysis of surface EMG signals should be lower not only in diagnosis of myopathy but also neuropathy.

Keywords: Turns analysis; Interference EMG signal; Muscle fatigue; Intracellular action potential

1. Introduction

Turns analysis is one of the oldest and most widely used methods for quantitating the electromyographic (EMG) interference signals in clinical studies [1–3]. Needle EMG is more often used in such studies. Despite of well-known advantages, needle EMG is also associated with significant problems. Pain, limited use in children and difficulties for use in follow-up studies are among them. Thus, the interest to non-invasive application of this method is natural [4,5]. The turn is defined as an independent of the baseline potential reversal that exceeds an established threshold [3]. The most frequently used threshold is 100 μV but 50 and 10 μV are also applied [4,6,7]. Upon non-invasive surface detection, a relative threshold (0.5 and 1% of full-scale deflection) is also used [4,5]. The first turn could be determined in relation to either the beginning of the signal or the first local extremum, whereas the last found turn is used as a benchmark for the subsequent one. The number of turns (NTs) per unit time (second) and mean turn amplitude (MTA) as well as their derivative characteristics are considered as valuable diagnostic tools in distinguishing between normal subjects and patients with myopathic or neuropathic disorders [8–13]. It is generally accepted that in neuropathy, the NTs is decreased whereas MTA is increased, while the opposite should be true in myopathy.

A number of authors [6,8,9,14] recommended performing analysis of turns at lower, 10–30% of maximum voluntary contraction (MVC) effort levels, because the results could be unreliable at higher levels of muscle activity. The turns analysis at a given force level requires cooperation of the patient; supporting a given force level correctly is time-consuming and almost impossible for some muscles [11]. Therefore, several modifications of turns–amplitude analysis disregarding estimation of muscle force have been suggested. It was proposed [15] to analyze a plot of MTA as function of NTs (the turns–amplitude cloud) without measurements of force. Another suggestion was the peak ratio, determined as the maximal value of the ratio between NTs and MTA during a gradual increase of force from zero to the maximum over 10–20 s [11]. Fuglsang-Frederiksen [11] considered that the cloud analysis and the peak ratio analysis have high diagnostic yield at higher efforts.

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ABSTRACT: Some myopathies are accompanied by abnormal calcium homeostasis. Electromyography (EMG) in such patients shows signs of normal or myopathic EMG when detected by a single-fiber electrode and abnormally increased values in macro EMG. As calcium accumulation might be accompanied by changes in intracellular action potential (IAP) and muscle-fiber propagation velocity, we simulated the effects of such changes on motor unit potentials (MUPs) recorded by different kinds of electrodes. We found that: (1) the requirements for what potential can be accepted as a single-fiber action potential (SFAP) are too rigorous; (2) macro MUP amplitude can increase while SFAP amplitude can decrease when there is an increase in the spatial length of IAP spike; and (3) changes in the second phase of a belly–tendon-detected MUP or M wave could be used for noninvasive detection of increased IAP depolarizing (negative) after-potential.
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EFFECTS OF CHANGES IN INTRACELLULAR ACTION POTENTIAL ON POTENTIALS RECORDED BY SINGLE-FIBER, MACRO, AND BELLY–TENDON ELECTRODES

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By applying turns analysis to interference electromyographic (EMG) signals, Torbergsen et al.[64,65] found clear myopathic changes in the biceps brachii of patients in the early stages of Marinesco–Sjögren syndrome as well as in the biceps brachii and tibialis anterior of patients with mitochondrial cytopathy. However, the size of macro motor unit potentials (MUPs) was significantly increased. This is more typical for neurogenic disorders, whereas normal or small macro MUPs are usually associated with myopathy.[33] Macro MUPs were increased even though the amplitudes of MUPs detected by concentric needle electrode and fiber density were normal and there was no loss of small motor units (MUs).[64,65] Thus, it is unclear why macro MUPs were increased. Nandedkar et al.,[46] Fawcett et al.,[18] and Finsterer and Fuglsang-Frederiksen[20,21] also observed increased amplitude or area of MUPs detected by concentric needle or macro EMG electrodes in a few patients with myopathy, but this finding remained unexplained. Thus, besides the typical findings of low-amplitude and short-duration MUPs that have been interpreted as signs of loss of muscle fibers,[59] other changes could also occur in myopathy.

In line with the widespread hypothesis about the cause for alterations of intracellular action potential (IAP) during fatigue,[19] Ludin[41] related the changes in IAP in dystrophic muscles to a decrease of potassium and an increase of sodium ion concentrations in muscle fibers. The effect of calcium accumulation was not involved. It is, however, known that intracellular free concentration of calcium ($[Ca^{2+}]_i$) is elevated in muscle fibers of patients with Duchenne muscular dystrophy.[3–5,17,25,31,35,36,43,53,66,67,72] On the other hand, IAP spike duration and negative (depolarizing) after-potential increased,[37] while muscle-fiber propagation velocity (MFPV) decreased[34] in a solution with increased calcium concentration. These changes in IAP shape strongly resemble those observed during fatigue of healthy fibers,[2,32,39,42,44,55] in which the resting intracellular calcium was also elevated.[27,28,68–71] Actually, the reduction of MFPV was a secondary effect following the primary one of

Abbreviations: $[Ca^{2+}]_i$, free calcium in muscle fibers; EMG, electromyography; IAP, intracellular action potential; MFPV, muscle-fiber propagation velocity; MU, motor unit; MUP, motor unit potential; SF single fiber; SFAP, single-fiber action potential

Key words: belly–tendon detection; calcium; myopathy; macro EMG; muscular dystrophy; neuropathy; SFAP

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ABSTRACT: The influence of changes in the intracellular action potential (IAP) spatial profile on motor unit potentials (MUPs), number of turns per second (NTs), and mean turn amplitude were simulated and analyzed. We show why measurement of NTs was "the best indicator of neurogenic affection" and why the lower diagnostic yield of turns/amplitude analysis in myopathy could be due to changes in IAP shape caused by elevated free calcium concentration. The results explain the complications observed when interference electromyographic signals obtained during high levels of isometric contractions were analyzed. We show that, in contrast to earlier assumptions, the effect of increased IAP spike duration on NTs was stronger than that of a decrease in muscle fiber propagation velocity (MFPV). The decrease in the NTs could occur without a drop-out of MUs and/or a decrease in their firing rates, and without a change in MFPV and synchronous firing.

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CHANGES IN INTRACELLULAR ACTION POTENTIAL PROFILE AFFECT PARAMETERS USED IN TURNS/AMPLITUDE ANALYSIS

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Quantitative electromyography (EMG) most often includes analysis of motor unit potentials (MUPs) or turns/amplitude analysis of the interference pattern.[24] A major drawback to analysis of MUPs detected directly without decomposition[8,59] is that they have to be recruited at weak effort at an average of 4% (range, 0%–20%) of the maximal voluntary contraction (MVC).[26] At higher efforts, the MUPs overlap, resulting in an interference pattern. This limits the examined motor units (MUs) to those recruited at low force. If only MUs recruited at higher effort are affected, the disease will not be revealed.[26] Some investigators recommend lower effort levels (10%–30% of MVC) for better discrimination of myopathic muscles when using turns/amplitude analysis.[19,20,32]

Turns analysis was introduced by Willison,[71], Fitch,[17] and Rose and Willison[56] to analyze interference EMG signals. A turn was defined as an independent-of-the-baseline potential reversal that differs from the previous and subsequent turns with a defined threshold (usually 100 μV).[56] The number of turns (NTs) per unit of time (seconds) and mean turn amplitude (MTA) as well as their derivative characteristics were used in several turns analysis methods (turns/amplitude analysis, peak ratio analysis, cloud analysis, etc.) claiming to diagnose neuromuscular disorders successfully. Turns analysis was believed to be a valuable diagnostic tool in distinguishing between normal subjects and patients with neuromuscular disorders, both myopathic and neuropathic.[16,19,20,22,26,33,61]

Neuropathy is often associated with loss of motor neurons combined with reinnervation of denervated muscle fibers from surviving motor neurons.[12,15,72] Due to collateral sprouting, the number of muscle fibers, fiber density, and variability in fiber diameters are increased in the remaining MUs.[35] As a result, the force and MUPs that the reinnervated MUs produce are larger compared with those in healthy subjects, and fewer MUs are necessary to maintain a required level of force. Thus, the NTs should be reduced, whereas the MTA should be enlarged in neuropa-

Abbreviations: $[Ca^{2+}]_i$, free calcium concentration in muscle fibers; EMG, electromyographic; IAP, intracellular action potential; MFPV, muscle fiber propagation velocity; MTA, mean turn amplitude; MU, motor unit; MUP, motor unit potential; MVC, maximal voluntary contraction; NTs, number of turns per unit time; SFAP, single-fiber action potential

Key words: interference EMG signal; myopathy; neuropathy; turns analysis

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A POSSIBLE LINK OF OXALIPLATIN-INDUCED NEUROPATHY WITH POTASSIUM CHANNEL DEFICIT

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ABSTRACT: *Introduction*: The neurotoxic side effects of oxaliplatin (a reference drug in the treatment of digestive tract tumors) can force suspension of treatment. The mechanisms of neuropathy are unclear. We aimed to simulate oxaliplatin-induced hyperactivity in myelinated axons (MA) based on published experimental data. *Methods*: A Hodgkin–Huxley-type multi-cable MA model was used, which took into account active internodal processes and accumulation of ions in MA with 21 nodes. *Results*: Even a very short (110–220 μm) internodal region devoid of potassium channels was sufficient to produce after-discharges in response to a saltatory action potential. An increase in the density of sodium channels, slowdown of their inactivation, and negative shifts along one node–internode region of the voltage dependence of sodium and potassium activation and of sodium inactivation induced no after-discharge. *Conclusion*: A combination of sodium channel blockers with drugs that obstruct the blockage of potassium channels or contribute to their opening could be effective in preventing oxaliplatin-induced 'hyperexcitability.'

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Colon cancer is the second leading cause of cancer death worldwide.[1] Oxaliplatin is a reference drug in the treatment of digestive tract tumors, especially advanced stage colorectal cancer.[2–4] Oxaliplatin has only mild hematological and gastrointestinal side effects. A decreased likelihood of developing drug resistance makes oxaliplatin a good candidate for first-line therapy.[5]

Despite the drug's advantages, oxaliplatin administration is complicated by prominent dose-limiting neurotoxicity that is unique among platinum analogs. The adverse effect of oxaliplatin is a severe and painful peripheral neuropathy that affects both sensory[6–11] and motor[9,10,12–14] nerve fibers. Distinctive acute and chronic side effects have been recognized.

At the completion of prolonged treatment, all patients had signs of severe (20%), moderate (51%), or mild (29%) neurotoxicity.[9] Neurotoxic symptoms necessitated a reduction of oxaliplatin dose in 43% of patients, whereas 37% of patients ceased the treatment prematurely. Neurotoxicity may progress for several months after cessation of treatment.[15] The chronic neuropathy is cumulative and may cause superficial and deep sensory loss, sensory ataxia, and functional impairment.[2,6,7,16–18] The chronic sensory neuropathy is of the axonal type with a reduction in compound sensory nerve action potential amplitude and relative preservation[8] or reduction[19] of nerve conduction velocity. This type of neuropathy is related to changes induced by accumulation of platinum in the dorsal root ganglion.[19]

Acute sensorimotor neuropathic symptoms include prominent cold-associated paresthesia, jaw tightness or pain, and muscle cramp or fasciculations. The symptoms develop immediately after infusion. Acute oxaliplatin-induced neurotoxicity has been associated with significant peripheral nerve hyperexcitability, suggesting a pharmacological rather than structural basis for acute symptoms.[8] Signs of hyperexcitability usually pressume an altered state of sodium channels. Indeed, different *in vivo* human studies[8,9,20] and *in vitro* studies of rat axons and neurons,[21] cockroach neurons,[22] frog axons,[23] and neuromuscular junctions of mouse diaphragm[13] suggested malfunctions of voltage-gated sodium channels. Positive effects of drugs known to act as sodium channel blockers, such as carbamazepine, seem to support these findings.[4,8,17,18,24] However, Lehky et al.[12] reported no effect of sodium channel blocker drugs on patients' symptoms. In fact, the available data on malfunction of sodium channels has also been shown to differ. Grolleau et al.[22] and Benoit et al.[23] noted considerable reduction in the sodium current with increasing oxaliplatin concentration and no changes in the shape of the current. Adelsberger et al.[21] explained the twofold increase in amplitude and duration of compound sural sensory nerve action potentials induced by oxaliplatin as a slowdown of the inactivation of sodium channels without effect on their activation. This implies changes in the shape of the sodium current in rat preparations. Kagiava et al.[25] found no effect on the amplitude and depolarization phase of the compound action potential and concluded that sodium channels were not affected by oxaliplatin in their sciatic nerve preparation. Benoit et al.[23] also reported oxaliplatin-induced negative shifts in the voltage dependence of

Abbreviations AP, action potential; FLUT, fluted paranodal segment; IAP, intracellular action potential; iAP, internodal action potential; $iAP_{(b)}$, internodal action potential back-propagating to nodes; $iAP_{(s)}$, internodal action potential induced by a salutatory action potential; L, length; MA, myelinated axon; MYSA, myelin sheath attachment segment; N, node; PN, paranode; sAP, salutatory action potential; STIN, stereotype internodal segment; T, temperature

Key words: hyperexcitability, myelinated axon model, oxaliplatin, potassium channels, sodium channels

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INTERNODAL MECHANISM OF PATHOLOGICAL AFTERDISCHARGES IN MYELINATED AXONS

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ABSTRACT: *Introduction:* Recent optical recordings of transmembrane potentials in the axons of pyramidal neurons have shown that the internodal action potentials (APs) predicted in our previous studies do exist. These novel processes are not well understood. In this study we aim to clarify electrical phenomena in peripheral myelinated axons (MAs). *Methods:* We used a multi-cable Hodgkin–Huxley-type model to simulate MAs with potassium channels that were either normal or inhibited along a short region of the internodal membrane. A brief stimulus was applied to the first node. *Results:* We demonstrated peculiarities in the internodal APs induced by a saltatory AP: They existed across internodal membranes, were detectable in periaxonal space but not in intracellular space, propagated continuously, collided near the mid-internodes, and produced internodal sources of afterdischarges. *Conclusions:* These results highlight the importance of the MA internodal regions as new therapeutic targets for avoiding afterdischarges provoked by reduced axonal fast potassium channel expression.

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Afterdischarges, that is, continued spiking after a brief stimulus, are known to occur under normal and pathological conditions.[1–3] The nature of these afterdischarges remains poorly understood. Under certain conditions, neurons generate single action potentials (APs) at the initial segment of the axon. For neuronal burst firing, the axonal sodium channels at the first node of Ranvier are also essential.[3] However, afterdischarges can originate within peripheral myelinated axons (MAs),[4–8] even though these MAs generally function in rapid signal conduction. What could a brief stimulus or single spike be altering in a peripheral axon to induce the afterdischarge regimen generally interpreted as a sign of axonal hyperexcitability[9–11]? Because the excitability of a cell is related to sodium channel activity, research into the source of new spikes or afterdischarges is generally focused on sites with high concentrations of sodium channels. Nodes of Ranvier are such candidate sites in peripheral MAs. Regions of excitable structures with low densities of sodium channels are usually ignored.

Our earlier theoretical studies[12] predicted that a source of afterdischarges could be created in the internodal region of MAs, where the density of sodium channels is only 2–6% of the sodium channel density in nodal regions.[13–17] If the width of the periaxonal space in a large-diameter MA is <400 nm, a saltatory AP (sAP) can induce internodal APs (iAPs).[18] This condition is easily satisfied, because the periaxonal space is usually only a few nanometers wide in a peripheral MA with normal myelination.[19] When the internodal regions are devoid of potassium channels, the iAPs can create internodal sources of afterdischarges.[12]

Experimental detection of the active internodal processes predicted in our theoretical studies is potentially problematic. The iAPs may be detected along with periaxonal or transmembrane potentials,[12] which are undetectable with classical microelectrode techniques used to record intracellular potentials. A high-sensitivity transmembrane potential imaging technique was recently used by Popovic *et al.*[20] to directly determine the location and length of the spike trigger zone in layer 5 pyramidal neurons. The high spatial resolution of the technique allowed them to simultaneously record transmembrane potentials as a function of time at numerous points along the proximal axon. Although iAPs were outside the main scope of their study, the investigators recorded internodal transmembrane APs with temporal characteristics similar to those of nodal APs.[20] To verify that the recorded signals were from an MA, they demonstrated differences in propagation of APs in myelinated and unmyelinated axons. The nature of the iAPs was not discussed.

Better understanding of these processes is important for comprehension of MA function and discovery of new therapeutic targets. Therefore, we aimed to clarify the sequence of electrical phenomena in peripheral MAs induced by a brief stimulus and discuss their importance in terms of health and disease. We have already described some peculiarities in the processes activated during the production of afterdischarges in MAs lacking potassium channels along the internodes and related them to neuromyotonia.[12] Signs of axonal

Abbreviations: ALS, amyotrophic lateral sclerosis; AP, action potential; iAP, internodal action potential; $iAP_{(b)}$, internodal action potential that back-propagates from an internode toward the closest node; $iAP_{(s)}$, internodal action potential induced by a saltatory action potential; MA, myelinated axon; sAP, saltatory action potential

Key words: afterdischarge; hyperexcitability; internode; potassium channel; simulation

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Chapter III

Axonal Afterdischarges: Problems and Mechanisms

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Abstract

Afterdischarges, i.e., continued spiking of an excitable structure after a brief stimulus, are known to occur under normal and pathological conditions. Production of afterdischarges is generally interpreted as a sign of cellular hyperexcitability. Excitability is associated with the activity of sodium channels; therefore the source of hyperexcitability is traditionally searched at the sites with high density of sodium channels. As afterdischarges can originate within peripheral myelinated axons (MAs), the nodes of Ranvier are under special attention of researchers. Nevertheless, the nature of afterdischarges remains poorly understood. We demonstrate an untraditional internodal mechanism of pathological axonal afterdischarges. The density of sodium channels within the internodal membrane of MAs is only 2-6% of the nodal density. Therefore, investigators ignore the internodes of MAs. However, our theoretical studies show that the ability of the structure to generate action potentials (APs) is not related directly to the density of sodium channels. When the volume conductor around the membrane is restricted as is in the case of a periaxonal space of small width, the internodal membrane

becomes able to generate internodal APs (iAPs) irrespective of the low density of sodium channels there. Thus, in response to an AP that propagates saltatory along the fiber, an iAP is produced in each of the two internodes located adjacent to the active node. They propagate continuously to the mid-internode where they collide with the internodal waves produced by other neighboring nodes. Fast potassium channels that are responsible for the membrane repolarization are mainly located within the internodes. When a certain internodal region is deprived of fast potassium channels, as is found in a number of pathologies, this region cannot be repolarized in full. This region remains depolarized for a prolonged time and thus becomes a source of secondary iAPs. They back-propagate to the nearest nodes, activate them, and thus produce saltatory afterdischarges. Experimental detection of the active internodal processes predicted in our theoretical studies used to be problematic. This was because the iAPs may be recorded correctly along with transmembrane potentials, which are undetectable with the classic microelectrode technique. However, a transmembrane potential imaging technique of high spatial resolution, recently used for recordings in the normal MAs of pyramidal neurons, has made the iAP recordable. This convinces us that the active internodal processes predicted in our studies do exist and stimulates us to highlight problems and details of electrical phenomena in MAs that could be useful in studies of MAs in health and disease.

Introduction

Afterdischarges, that is, continued spiking after a brief stimulus, are known to occur under normal and pathological conditions [1-3]. The nature of these afterdischarges remains poorly understood. This brings up new questions on excitability, conditions for action potential (AP) initiation and sources and sites of AP initiation. The axon hillock is not considered as an exclusive site of impulse initiation anymore. The distal portion of the initial segment or even the first node of Ranvier [3-5] is reported to be an encoding site for repetitive firing in the central neurons. However, there are also data on the acquired peripheral nerve hyperexcitability syndrome [6-10], which show that repetitive activity can originate from myelinated axons (MAs) of peripheral nerves. These MAs are far from the axon hillock, and they generally function in rapid signal conduction. What could a brief stimulus or single spike be altering in a peripheral axon to induce the afterdischarge regimen generally interpreted as a sign of axonal hyperexcitability [11-13]?