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Differences in potentials and excitability properties in simulated cases of demyelinating neuropathies. Part III. Paranodal internodal demyelination

D.I. Stephanova*, M. Daskalova

Institute of Biophysics, Bulgarian Academy of Sciences, Acad. G. Bontchev Str. Bl 21, Sofia 1113, Bulgaria

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Abstract

Objective: The aim of this study is to investigate the potentials (intracellular, extracellular, electrotonic) and excitability properties (strength–duration and charge–duration curves, strength–duration time constants, rheobasic currents, recovery cycles) in progressively greater degrees of uniform reduction (20, 50 and 70%) of the paranodal seal resistance and myelin lamellae along the fibre length.

Methods: Three paranodally internodally systematically demyelinated cases (termed as PISD1, PISD2 and PISD3, respectively) are simulated using our previous double cable model of human motor nerve fibres.

Results: The results conform that in the more severely demyelinated cases, the intracellular potentials are with significantly reduced amplitude, prolonged duration and slowed conduction velocity, whereas the electrotonic potentials show abnormally greater increase in the early part of the hyperpolarizing responses. The extracellular potentials indicate increased polyphasia in the PISD3 case. The strength–duration time constants are shorter and the rheobasic currents higher in the demyelinated cases. In the recovery cycles, the demyelinated cases have less refractoriness, greater supernormality and less late subnormality than the normal case.

Conclusions: The uniform reduction of the paranodal seal resistance and myelin thickness along the fibre length has significant effects on the potentials and excitability properties of the simulated demyelinated human motor fibres. Unexpectedly, the PISD fibres behave like paranodally demyelinated ones, since the myelin reduction increases slightly the effect of the paranodal demyelination on the nerve membrane properties. The study shows that the excitability properties in demyelinating neuropathies are much more largely determined by the paranodal changes than by the internodal changes.

Significance: The study provides new and important information about the pathophysiology of human demyelinating neuropathies.

Keywords: Chronic inflammatory demyelinating polyneuropathy; Charcot–Marie–Tooth disease type 1A; Computational neuroscience; Potentials; Excitability properties

1. Introduction

Charcot–Marie–Tooth disease type 1A (CMT1A) is the most common form of hereditary motor and sensory neuropathy and its hallmark is uniform demyelination (Birouk et al., 1997; Dyck et al., 1993). Moreover, chronic inflammatory demyelinating polyneuropathy (CIDP) is one of several chronic demyelinating neuropathies that are believed to have an autoimmune etiology. CIDP can occur with other systemic diseases (Barohn et al., 1989; Gorson et al., 2000; Katz et al., 2000) and there are subtypes of chronic demyelinating neuropathies (Alaedini et al., 2003; Alexandrov et al., 2001; Alaedini et al., 2003; Christova et al., 1999; Christova et al., 2001; Katz et al., 1997; Katz et al., 2000; Krarup et al., 1990; Lewis et al., 1982;) that are broadly classified under the term of CIDP. Accuracy in establishing the diagnosis in nerve disorders, such as CMT1A and CIDP is related particularly to the appropriate application of electrodiagnostic techniques. These include motor and sensory conduction studies, late responses (F-wave and H reflex), blink reflexes, sympathetic skin

* Corresponding author. Tel.: +359 2 9792127; fax: +359 2 9712493.
E-mail address: dsteph@iph.bio.bas.bg (D.I. Stephanova).

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potentials, threshold tracking studies and needle electromyography. Using the technique of threshold tracking, the indices of the axonal excitability, such as electrotonic potentials, strength–duration time constants, rheobasic currents and recovery cycles can now be measured in healthy subjects and patients with nerve disorders (Bostock et al., 1995; Cappelen-Smith et al., 2001; Kuwabara et al., 2002; Kuwabara et al., 2003; Mogyoros et al., 1998; Nodera et al., 2004; Sung et al., 2004). The studies show that in CMT1A and CIDP patients, the threshold electrotonus changes are greater in response to hyperpolarizing stimuli (Nodera et al., 2004; Sung et al., 2004) and the axonal excitability properties are also abnormal (Cappelen-Smith et al., 2001). These include longer or shorter strength–duration time constants, less refractoriness and less or greater supernormalities in CIDP and CMT1A patients than in the normal subjects. In the recent years, mathematical simulations are also applied for studying the mechanisms of human nerve disorders (Stephanova, 1989a,b; Stephanova, 1990; Stephanova and Chobanova, 1997; Stephanova and Daskalova, 2002; 2003, 2004; Stephanova and Kossev, 1997; Stephanova et al., 2001). The results indicate that the potentials and excitability properties depend not only on the electrophysiological cable characteristics of the axolemma and myelin sheath but also on the methods of fibre stimulation.

To investigate and analyze the nature of the abnormalities in the excitability and potentials in three paranodally internodally systematically demyelinated cases of human motor nerve fibres, we have used the method of mathematical modeling and have applied appropriate stimulated methods for the fibres. The results are consistent with the interpretation that the factors causing a uniform reduction of the myelin sheath and paranodal seal resistance could be responsible for the obtained abnormalities.

2. Methods

2.1. Double cable model

The intracellular and electrotonic potentials of human myelinated nerve fibre can be studied successfully using the described earlier double cable model of human motor fibre (Stephanova and Bostock, 1995; Stephanova and Bostock, 1996). The interested reader is referred to Fig. 1 of Stephanova and Bostock (1995) for an electric equivalent circuit representation of the fibre. In the cited paper, Kirchoff's current law is used to derive a system of partial differential equations for the electric equivalent circuit. The latter is based on a complex extended double cable structure of nodal, paranodal and internodal segments with their corresponding ion (nodal and internodal) channels. The ion channel types demonstrated in mammalian myelinated axons and their maximal permeabilities are taken from a two-component (node + internode) model of human motor axons (Bostock et al., 1991). The membrane parameter values of the double cable model are adjusted to match, both the recordings of threshold electrotonus from Bostock et al. (1991, 1994) and the recordings (Dioszeghy and Stålberg, 1992) of intracellular potentials with their parameters (amplitude, depolarizing afterpotential, duration and conduction velocity) in human motor nerves. The model assumes a high-resistance myelin sheath and a leakage pathway to the internodal axolemma via the paranodal seal resistance and periaxonal space. The same model is used here to simulate paranodal internodal systematic demyelinations, which are defined as an uniform reduction (20, 50 and 70%) of the paranodal seal resistance and myelin lamellae along the fibre length. The paranodally internodally systematically demyelinated cases are termed as PISD1, PISD2 and PISD3, respectively. In the normal fibre, the R_{pn} (paranodal seal resistance) is 125 MΩ and the fibre has $N = 150$ myelin lamellae. Its myelin sheath is characterized with C_{my} (myelin capacitance) 1.5 pF and R_{my} (myelin resistance) 250 MΩ. Each parameter value for a given myelin spiral differs in arithmetic progression with N. The rule of the arithmetic increasing or decreasing of the value, however, depends on the type of the given parameter. For the PISD1 case the myelin parameter values and the value of the paranodal resistance are $N = 120$, $C_{my} = 1.8$ pF, $R_{my} = 200$ MΩ and $R_{pn} = 100$ MΩ. For the PISD2 case they are $N = 75$, $C_{my} = 3.0$ pF, $R_{my} = 125$ MΩ, $R_{pn} = 62.5$ MΩ and for the PISD3 case they are $N = 47$, $C_{my} = 4.8$ pF, $R_{my} = 78.3$ MΩ, $R_{pn} = 39$ MΩ. The simulated demyelinations are associated with a corresponding loosing or lifting of the myelin lamellae with their myelin end-bulbs away from the paranodal axolemma. The other membrane parameter values for the motor fibre are the same as described earlier (Stephanova and Bostock, 1995; Stephanova and Mileva, 2000). The model fibres comprise 30 nodes of Ranvier and 29 internodes. All calculations are carried out for fibre with an axon core diameter of 12.5 μm. The lengths of node, paranode and nodal center to nodal center are 1.5, 200 and 1400 μm, respectively. The temperature is 37 °C. The normal myelin thickness of 2.4 μm gives an external fibre diameter of 17.3 μm. In the investigated demyelinated cases both the myelin thickness and the external diameter are reduced and the reduction depends on the degree of demyelination.

2.2. Stimulations

The stimulation, to produce intracellular potentials, is simulated by adding a short (0.1 ms) rectangular threshold current pulse to the center of the first node. This case of intracellular point current application at the center of the node closely approximates the effects of external point stimulation with a needle electrode and realizes a point fibre polarization. The intracellular potentials in the case of adaptation (i.e. in the case of simultaneously intracellular current application at the midpoints of all the available