ELSEVIER

Clinical Neurophysiology 116 (2005) 1159–1166

www.elsevier.com/locate/clinph

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

D.I. Stephanova*, M. Daskalova

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

Accepted 13 January 2005

Abstract

Objective: The purpose of the present investigation is to study the potentials and axonal excitability properties in progressively greater degrees of uniform paranodal demyelination of human motor nerve fibres.

Methods: Using our previous double cable model of human motor nerve fibre, 3 paranodally systematically demyelinated cases (termed as PSD1, PSD2 and PSD3) are simulated by an uniform paranodal resistance reduction (20, 50 and 77%) along the fibre length.

Results: Considerably reduced amplitudes, prolonged durations and slowed conduction velocities are obtained for the intracellular potentials of the PSD2 and PSD3 cases. In contrast, the electrotonic potentials show abnormally greater increase in the early part of the hyperpolarizing responses. The extracellular potentials indicate increased polyphasia in the PSD3 case. The strength–duration time constants are shorter and the rheobases 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 reduction of the paranodal seal resistance has significant effects on the potentials and axonal excitability properties of the simulated demyelinated human motor fibres. The obtained abnormalities in the potentials and excitability properties can be observed in vivo in patients with chronic inflammatory demyelinating polyneuropathy.

Significance: The study provides important information about the pathology of human demyelinating neuropathies.

Keywords: Chronic inflammatory demyelinating polyneuropathy; Computational neuroscience; Potentials; Strength–duration properties; Recovery cycle

1. Introduction

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, 2003; Christova et al., 1999, 2001; Katz et al., 1997, 2000; Krarup et al., 1990; Lewis et al., 1982) that are broadly classified under the term of CIDP. These include sensory CIDP, multifocal motor neuropathy (MMN) with or without conduction block, multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy, distal acquired demyelinating sensory (DADS) neuropathy and multifocal acquired sensory and motor (MASAM) neuropathy. Unfortunately, because of the lack of clarity with regard to diagnostic criteria (clinical, serologic and electrophysiologic) for CIDP, many patients remain untreated. In the recent years, using the threshold-tracking system (non-invasive technique of threshold electrotonus), the excitability properties of human nerves are recorded from patients with nerve disorders (Bostock et al., 1995; Cappelen-Smith et al., 2001; Kuwabara et al., 2002, 2003; Nodera et al., 2004; Sung et al., 2004) and compared with those of healthy controls. The studies show that in CIDP patients, the threshold electrotonus changes are abnormally greater in response to hyperpolarizing stimuli (Sung et al., 2004) and the axonal excitability properties are also abnormal (Cappelen-Smith et al., 2001). These include shorter

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

1388-2457/$30.00
doi:10.1016/j.clinph.2005.01.005

strength–duration time constant, less refractoriness and less or greater supernormality in CIDP patients than in the normal subjects. Also, in the recent years, mathematical simulations are applied for studying the mechanisms of human nerve disorders (Stephanova, 1988a,b,c, 1989a,b, 1990; Stephanova and Chobanova, 1997; Stephanova and Daskalova, 2002, 2003, 2004; Stephanova and Kossev, 1996; 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.

The aim of this study is to investigate the abnormalities in the potentials and excitability properties of 3 simulated cases of paranodally systematically demyelinated axons applying appropriate stimulated methods for the human fibres. The results are consistent with the interpretation that the morphological factors causing changes in the paranodal segments could be responsible for the obtained abnormalities.

2. Methods

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, 1996). The interested reader is referred to Fig. 1 of Stephanova and Bostock (1995) for an electric equivalent circuit representation of the fibre. The electric equivalent circuit 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, depolarising 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 systematic paranodal demyelinations, which are defined as an uniform reduction (20, 50 and 77%) of the paranodal seal resistance along the fibre length. The paranodally systematically demyelinated types are termed as PSD1, PSD2 and PSD3, respectively. The paranodal seal resistance is 125 MΩ for the normal fibre. The values for the same resistance are 100, 62.5 and 29 MΩ for the PSD1, PSD2 and PSD3, respectively. The value of 29 MΩ is the final decreased resistance value for the demyelinated case, after which the conduction block is obtained. The simulated demyelinations are associated with a corresponding loosing or lifting of the 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 stimulation, to produce intracellular potentials is simulated by adding a short (0.1 ms) rectangular threshold current pulse to the centre of the first node. This case of intracellular point current application at the centre 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 axonal segments) are simulated by adding a long-lasting suprathreshold depolarising pulse. This case closely approximates the effects of external surface stimulation with a large electrode and realizes a periodic kind of uniform fibre polarization. The periodic kind of uniform polarization is first simulated by Stephanova and Bostock (1996) in the human motor electrotonus model. The generated intracellular potentials in the second case of fibre stimulation are then used as input to a line source model (Stephanova et al., 1989) that allows calculating of the corresponding extracellular potentials at various radial distances in the surrounding volume conductor. The electrotonic potentials are simulated by adding 100 ms subthreshold (±40% of threshold) polarizing current pulses to the centre of each axonal segment and the case of periodic kind of uniform fibre polarization is realized. The electrotonic potentials are presented for depolarising and hyperpolarizing currents, which correspond to 0.4 times the threshold for a 1 ms current pulse.

The indices of the axonal excitability delivered from single or pairs of threshold stimuli (such as strength–duration and charge–duration curves, strength–duration time constants, rheobasic currents and recovery cycles) are investigated in the case of periodic kind of uniform fibre polarization. The strength–duration time constants and rheobasic currents are calculated by the method, which is described earlier (Daskalova and Stephanova, 2001; Stephanova and Daskalova, 2004) and, in brief, the threshold stimulus duration is increased in 0.025 ms steps from 0.025 to 1 ms, to obtain the strength–duration curves. A polynomial function of degree 2 (transfer standard parabola), which relates threshold charge (Q) to stimulus duration (t), provides an accurate fit of the data: $Q = a_2[t^2 + (a_1/a_2)t + a_0/a_2]$, where a_0, a_1, a_2 are the polynomial coefficients. The strength–duration time constant is defined as the absolute value of the smallest square root of the function (i.e. only one of both direct intercepts of the regression curve on the duration axis has a biophysical sense and only this direct intercept is shown on the below given figures). The rheobase is defined as the final decreased threshold value, after which the potential generation is not