

DC-Evoked Modulation of Excitability of Myelinated Nerve Fibers and Their Terminal Branches; Differences in Sustained Effects of DC

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Abstract—Direct current (DC) evokes long-lasting changes in neuronal networks both presynaptically and postsynaptically and different mechanisms were proposed to be involved in them. Different mechanisms were also suggested to account for the different dynamics of presynaptic DC actions on myelinated nerve fibers stimulated before they entered the spinal gray matter and on their terminal branches. The aim of the present study was to examine whether these different dynamics might be related to differences in the involvement of K⁺ channels. To this end, we compared effects of the K⁺ channel blocker 4-amino-pyridine (4-AP) on DC-evoked changes in the excitability of afferent fibers stimulated within the dorsal columns (epidurally) and within their projection areas in the dorsal horn and motor nuclei (intraspinally). 4-AP was applied systemically in deeply anesthetized rats. DC-evoked increases in the excitability of epidurally stimulated afferent nerve fibers, and increases in field potentials evoked by these fibers, were not affected by 4-AP. In contrast, sustained decreases rather than increases in the excitability of intraspinally stimulated terminal nerve branches were evoked by local application of DC in conjunction with 4-AP. The study leads to the conclusion that 4-AP-sensitive K⁺ channels contribute to the sustained DC-evoked post-polarization increases in the excitability at the level of terminal branches of nerve fibers but not of the nodes of Ranvier nor within the juxta-paranodal regions where other mechanisms would be involved in inducing the sustained DC-evoked changes. © 2018 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: myelinated nerve fibers, spinal cord, epidural stimulation, DC polarization, plasticity.

INTRODUCTION

Long-lasting facilitatory effects of direct current (DC) were most extensively investigated at the cortical level (for review see e.g., Nitsche et al., 2008; Stagg and Nitsche, 2011; Jamil et al., 2017; Lefaucheur et al., 2017; Tang et al., 2017) but they were also found in other structures (for references see e.g., Jankowska, 2017; Rahman et al., 2017) and irrespective of whether DC was applied as diffuse current flow in considerable regions of the nervous system (see Rahman et al., 2017) or as locally as possible (see Jankowska, 2017), trans-cranially (tDCS), trans-spinal (tsDCS), locally (locDC), or in vitro. Within each of the explored regions, presynaptic actions of DC were shown to be as important as or even more important than postsynaptic actions. This was demonstrated during DC application (Bikson et al., 2004; Radman et al., 2009;

Kabakov et al., 2012; Bikson et al., 2013; Rahman et al., 2013, 2017) as well as during several tens of minutes of the post-polarization periods (Bolzoni et al., 2013; Ahmed, 2014; Baczyk and Jankowska, 2014; Bolzoni and Jankowska, 2015).

Furthermore, the post-polarization increases in the excitability of afferent fibers were detected not only within terminal projections areas of these fibers but also within the dorsal columns, i.e., before they entered the gray matter (see Jankowska et al., 2017) and in peripheral nerves (Ardolino et al., 2005; Ahmed, 2014; Bolzoni et al., 2017). However, major differences have been found in the dynamics of DC effects on various compartments of afferent fibers. Post-polarization increases in the excitability of epidurally polarized fibers in the dorsal columns appeared within seconds and did not require prolonged DC application (Jankowska et al., 2017), while intraspinally and transcortically or transspinally evoked actions develop slowly, require several minutes lasting polarization, and often reach the maximum within tenths of minutes after the termination of DC (see e.g., Nitsche and Paulus, 2000). These differences raised the question of whether different mechanisms might underlie actions of DC on

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Abbreviations: 4-AP, 4-amino-pyridine; DC, Direct current; locDC, locally; Per, peroneal; Sur, sural; tDCS, trans-cranially; tsDCS, trans-spinal.

myelinated fibers in the dorsal columns and on unmyelinated preterminal compartments of these fibers.

In the present study, this question was addressed by examining *the involvement of K^+ channels in the long-lasting epidural and intraspinal effects of DC*. This was done by comparing DC effects under conditions when these channels were blocked by the K^+ channel blocker 4-amino-pyridine (4-AP).

The experiments were carried out in rats under pentobarbital/chloralose anesthesia in which cathodal DC was applied either epidurally (Jankowska, 2017; Jankowska et al., 2017) or intraspinally (Bolzoni and Jankowska, 2015). 4-AP was injected systemically (Jankowska et al., 1977, 1982) or ionophoretically within the terminal projection areas of skin and muscle afferents in the dorsal horn and in motor nuclei. Following application of 4-AP the excitability of the tested fibers was increased, whether the fibers were stimulated epidurally or intraspinally, in keeping with depolarizing actions of 4-AP. However, 4-AP was found to interfere with DC-evoked modulation of the excitability of epidurally and intraspinally stimulated fibers in a markedly different manner. 4-AP did not modify the fast-developing and long-lasting DC-evoked increases in the excitability of myelinated fibers within the dorsal column while the 4-AP application was followed by a slowly developing decrease, rather than an increase in the excitability of terminal branches of skin and muscle afferents by their polarization in the dorsal horn and motor nuclei.

EXPERIMENTAL PROCEDURES

Ethical approval

All experiments were approved by the Regional Ethics Committee for Animal Research (Göteborgs Djurförsöksetiska Nämnd) and followed EU and USA guidelines for animal care. The animals were bred and housed under veterinary supervision at the Laboratory of Experimental Biomedicine at Sahlgrenska Academy where the experiments were carried out and particular measures were taken to minimize the animal discomfort and to minimize the number of animals used.

Preparation

The experiments were performed on 25 adult rats of both sexes (Wistar, 250–450 g) using the same general procedures as Bolzoni and Jankowska (2015) and Jankowska et al. (2016). Anesthesia was induced with isoflurane (4% in air) (Baxter Medical AB, Kista, Sweden) followed by i.p. administration of α -chloralose (Acros Organics, Geel, Belgium, (30–40 mg/kg) together with pentobarbital sodium (Apoteksbolaget, Göteborg, Sweden) (15 mg/kg). During the course of the experiment, the anesthesia was supplemented with 3–4 additional doses of α -chloralose (10 mg/kg up to 60–80 mg/kg) at 2–3 h intervals, and if the continuously monitored heart rate increased above 400 bpm. The preliminary dissection under full deep surgical anesthesia included tracheal

intubation, bilateral cannulation of tail veins, insertion of an intraperitoneal catheter, dissection of the peroneal (Per) and the sural (Sur) nerves as well as the exposure of the L2–L4 spinal segments by laminectomy. Paraffin oil pools were constructed by skin flaps above the dissected tissues. When the neuromuscular transmission was blocked by pancuronium bromide (Pavulon Jelfa, Poland) or by Gallamine triethiodide (Sigma–Aldrich, G8134), artificial ventilation was applied using a respiratory pump (CWE, model SAR-830/P; 50–70/min and 0.3–0.5 ml/min) to maintain the expired CO_2 level at 3–4%. Pancuronium and Gallamine were applied i.v. (via one of the vein catheters) using about 10 mg/kg initial dose supplemented when needed. The neuromuscular transmission was blocked a few hours after the induction of anesthesia, by which time the depth of anesthesia was stable. 4-AP (Sigma–Aldrich A78403) was applied via the 2nd vein catheter by injecting 0.3 mg/kg at the beginning of the experiment. The dose was supramaximal as similar effects were evoked by 0.1 mg/kg and effects of comparable doses of 4-AP on synaptic transmission in the cat were found to be retained for several hours (Jankowska et al., 1982).

The core body temperature was maintained at approximately 38 °C by servo-controlled heating lamps. In order to compensate for fluid loss and to prevent the deterioration of the state of the animals, 10–20 ml of acetate buffer was injected subcutaneously at the beginning of the experiments. The experiments were terminated by a lethal dose of pentobarbital followed by excision of the heart.

Recording

The effects of DC on the excitability of the afferent fibers were estimated from changes in their responses to near-threshold intraspinal stimuli applied within their terminal projection areas, or epidurally but at intensities restricting them to the dorsal column. The responses were recorded in the Per and/or Sur nerves as indicated in Fig. 1A, B. They were recorded di- or mono-phasically with a pair of silver/silver chloride electrodes in a paraffin oil pool. As the terminal projection areas of the afferents to be stimulated were selected the areas in which distinct monosynaptic field potentials and cell activity were evoked from the two nerves using the setup outlined in Fig. 1C. The field potentials were recorded with glass micropipettes filled with a 2 M solution of NaCl (approximately 2- μ m tip, impedance 1.5–5 M Ω) and a conventional high-impedance amplifier (low-pass filters 15 or 1 Hz, high-pass filter 5 or 3 kHz). Afferent volleys following nerve stimulation were recorded with a silver–silver chloride ball electrode in contact with the surface of the spinal cord at the L2 spinal level against a reference electrode inserted into the back muscles at the same segmental level. They were also recorded as triphasic or biphasic potentials preceding the extracellularly recorded field potentials. Both the original records and averages of records evoked by 10 stimuli were stored online.

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