Journal of Physiology - Paris xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Physiology - Paris

journal homepage: www.elsevier.com/locate/jphysparis

Functional monitoring of peripheral nerves from electrical impedance measurements

Alexandre Fouchard [a,b,c,*], Véronique Coizet [b,c], Valérie Sinniger [b,c], Didier Clarençon [b,c,d], Karin Pernet-Gallay [b,c], Stéphane Bonnet [a], Olivier David [b,c,*]

[a] CEA-LETI, MINATEC Campus, F-38000 Grenoble, France
[b] Univ Grenoble Alpes, Grenoble Institut des Neurosciences, GIN, F-38000 Grenoble, France
[c] Inserm, U1216, F-38000 Grenoble, France
[d] Institut de Recherche Biomédicale des Armées, F-91223 Brétigny-sur-Orge, France

ARTICLE INFO

Article history:
Received 30 June 2016
Received in revised form 5 March 2017
Accepted 26 May 2017
Available online xxxx

Keywords:
Neuromodulation
Electrical impedance
In vivo nerve monitoring
Adaptive stimulation
Electrode design
Electroneurogram

ABSTRACT

Medical electrical stimulators adapted to peripheral nerves use multicontact cuff electrodes (MCC) to provide selective neural interfaces. However, neuroprostheses are currently limited by their inability to locate the regions of interest to focus. Intended until now either for stimulation or recording, MCC can also be used as a means of transduction to characterize the nerve by impedancemetry. In this study, we investigate the feasibility of using electrical impedance (EI) measurements as an in vivo functional nerve monitoring technique. The monitoring paradigm includes the synchronized recording of both the evoked endogenous activity as compound action potentials (CAP) and the superimposed sine signal from the EI probe. Measurements were conducted on the sciatic nerve of rodents, chosen for its branchings towards the peroneal and tibial nerves, with both mono- and multi-contact per section electrodes. During stimulation phases, recordings showed CAP with consistent fiber conduction velocities. During coupled phases of both stimulation and sine perturbation, impedance variations were extracted using the mono-contact electrode type for certain frequencies, e.g. 2.941 kHz, and were temporally coherent with the previous recorded CAP. Using a MCC, localized evoked CAP were also recorded but the signal to noise ratio (SNR) was too low to distinguish the expected associated impedance variation and deduce an image of impedance spatial changes within the nerve. The conducted in vivo measurements allowed to distinguish both evoked CAP and associated impedance variations with a strong temporal correlation. This indicates the feasibility of functional EI monitoring, aiming at detecting the impedance variations in relation to neural activity. Further work is needed to improve the in vivo system, namely in terms of SNR, and to integrate new multicontact devices in order to move towards EI tomography with the detection of spatially-localized impedance variations. Eventually, regions that are interesting to be targeted by stimulation could be identified through these means.

1. Introduction

Neurostimulation is an alternative to pharmacological and conventional treatments of refractory neurological and psychiatric disorders, but is also applicable to other multiple disorders when considering stimulation of peripheral nerves. This is the case of vagus nerve stimulation, which is validated for epilepsy and depression but is also under clinical evaluation for the treatment of various diseases like inflammatory disorders, sepsis, headache or cardiovascular diseases (Bonaz et al., 2013). Medical electrical stimulators adapted to peripheral nerves use multicontact cuff electrodes (MCC) to provide selective neural interfaces. A current challenge in therapeutical neurostimulation is to know how to stimulate both spatially and temporally to obtain maximum efficacy in every subject. Performing adaptive stimulation would allow increasing the device autonomy, reducing side effects and enslaving stimulation settings within a feedback loop (Famm et al., 2013).

When dealing with peripheral nerve stimulation, neuroprostheses are currently limited by their inability to locate the bundles of interest for the stimulation, e.g. with projections to specific organs and/or functions. Current means of locating areas of interest include the study of the effect of the stimulation over physiological

* Corresponding authors at: Grenoble Institut des Neurosciences, Chemin Fortuné Ferrini – Bât EJ Safra – CHU, 38700 La Tronche, France.
E-mail address: Olivier.David@inserm.fr (O. David).

http://dx.doi.org/10.1016/j.jphysparis.2017.05.003
0928-4257/

markers such as the blood pressure or the heart rate variability (Plachta et al., 2014). Regarding the imaging of the peripheral nervous system, current trends include both anatomical and functional modalities. Anatomical imaging comprises high resolution neuroimaging techniques based on either magnetic resonance (Howe et al., 1992) or ultrasound (Üçeyler et al., 2016). Yet they are not able to provide access to the internal structure of nerves at the submillimeter scales in vivo. Functional imaging integrates both calcium imaging and electrical source localization. While calcium imaging is used to monitor transitory signals during evoked compound action potentials (CAP) of cortical neurons (Grienberger and Konnerth, 2012), it is currently not adapted for imaging within a nerve. Electric source localization from electroneurograms (ENG) has been adapted from electroencephalography (Tang et al., 2014; Zariffa and Popovic, 2009). The determination of the active zone using ENG suffers from high sensitivity to exogenous and biological noises. It is also limited in spatial resolution, and the identification problem has no unique solution. Thus, current peripheral nerve imaging techniques do not allow for obtaining spatially localized in vivo information, compatible with the order of magnitudes regarding spatial resolution of a few micrometers and temporal resolution of a few milliseconds.

Here, we investigate the feasibility of using electrical impedance monitoring (EIM) and electrical impedance tomography (EIT) from both mono- and multi-contact electrodes (Seo and Woo, 2013) as methods for functional characterization of peripheral nerves in vivo (Fig. 1). EIM/EIT offers a temporal resolution of the millisecond, a high sensitivity to electrical property contrasts and a higher number of independent measurements (Holder, 1987). As a soft-field modality, EIT infers conductivity maps from electrical boundary measurements. Facing the inner complexity of a nerve, the low spatial resolution of EIT may prove inadequate to provide precise anatomical information. The advent of multispectral EIT (Fouchard et al., 2016) may allow to infer the global structure of a nerve, e.g. fascicular positions and the presence of blood vessels. Regarding functional imaging, the rationale of EIM/EIT for neural imaging consists in detecting the impedance variation occurring during neuronal activity (Oh et al., 2011). Axonal depolarization indeed (i) induces the opening of the ionic channels which results in a decrease of the axonal membrane impedance up to 10% (Cole and Curtis, 1939); (ii) provides additional conductive ions for current propagation (Keynes and Lewis, 1951). For isolated neurons, action potential propagation produces a local impedance variation. But in practice, the net effect on the global nerve impedance is relatively low, of about 1%. This variation is somewhat very small and very rapid, which makes it difficult to measure. But if a neuron population is concerned, the impedance change during a coherent neuronal activity is more pronounced (Holder, 1992). Neural imaging using EIT has been considered for in vivo brain imaging (Aristovich et al., 2014) and for ex vivo studies for nerves of a few millimeters diameter (Aristovich et al., 2015). These authors proposed to explore the possibilities of EIT regarding in vivo peripheral nerve imaging practically in small animal experiments using functional EIT (fEIT).

The main goal of this study was to present the theory and feasibility of measuring the impedance variations that occurs when CAP propagate along the rat sciatic nerve in vivo (Žužek et al., 2017). This is the prerequisite for further imaging using existing reconstruction tools (Seo and Woo, 2013; Fouchard et al., 2016). Below, we detailed the experimental protocol for functional characterization of a peripheral nerve using EIM, including the animal preparation, the electrode configuration, the instrumentation setting, the recording parameters and the signal processing. We proposed preliminary benchmarks for CAP recordings using two characteristic sizes of electrode contacts. We also considered the measurement of impedance variations with varying frequency, which eventually inquired designs for microelectrodes which would be suitable for localized impedance variation recording and subsequent imaging using EIT. In addition, histological sections were obtained *ex vivo* to estimate the expected fiber conduction velocities.

2. Materials and methods

2.1. Theory

Measuring the impedance variation requires both to stimulate the nerve to trigger action potential propagation and to inject synchronously a small current perturbation to sense the impedance variation, in a 4 electrode setting (Fig. 2). The impedance variation comes along with the action potential (AP) propagation (Holder,

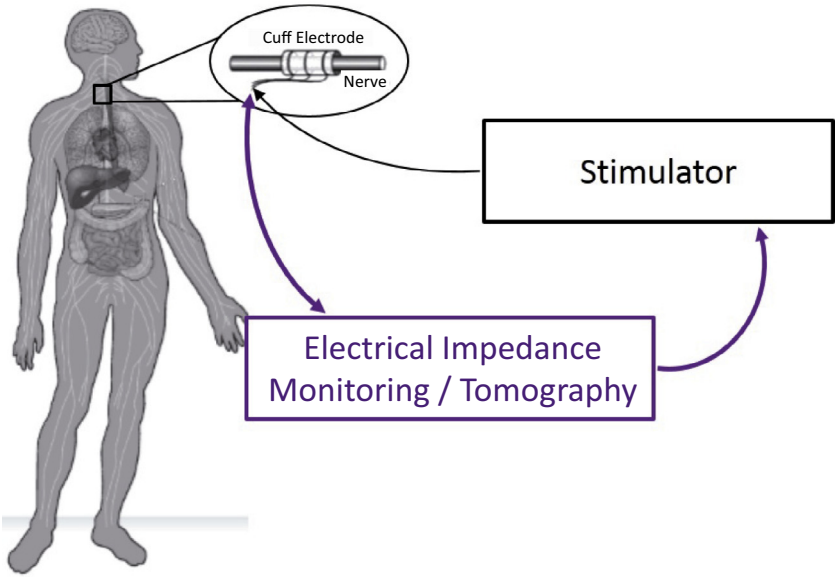

Fig. 1. Diagram of the feedback loop for adaptive stimulation using functional EIM/EIT. The multicontact cuff electrode implanted around the vagus nerve currently enables for both stimulation and activity recording. As a functional modality, EI/EIT is intended to provide specific information on the electric pathways within the nerve and should provide sufficient information to adapt the stimulation parameters and configurations.

Please cite this article in press as: Fouchard, A., et al. Functional monitoring of peripheral nerves from electrical impedance measurements. J. Physiol. (2017), http://dx.doi.org/10.1016/j.jphysparis.2017.05.003