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Separated Interface Nerve Electrode Prevents Direct Current Induced Nerve Damage

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Abstract

Direct current, DC, can be used to quickly and reversibly block activity in excitable tissue, or to quickly and reversibly increase or decrease the natural excitability of a neuronal population. However, the practical use of DC to control neuronal activity has been extremely limited due to the rapid tissue damage caused by its use. We show that a separated interface nerve electrode, SINE, is a much safer method to deliver DC to excitable tissue and may be valuable as a laboratory research tool or potentially for clinical treatment of disease.

Introduction

The delivery of biphasic electrical currents with implantable pulse generators is a well established laboratory technique and has been used clinically to treat cardiovascular and neurological diseases in millions of people to date (e.g. cardiac pacing, deep brain stimulation, spinal cord stimulation, cochlear implants, functional motor restoration, etc.) [1]. The delivery of monophasic direct current, DC, holds similar promise as both a laboratory and clinical therapeutic or diagnostic tool. While biphasic current is typically used to induce activity in excitable tissue, monophasic current can be used to quickly (msec) and reversibly block activity [2], or to quickly and reversibly increase or decrease the natural excitability of a neuronal population [3,4]. However delivery of DC to tissue quickly results in tissue damage [5–8]. Therefore it has been of only limited utility, restricted to use in a few laboratory preparations where the requirements for DC delivery are brief. A method of safely delivering DC to excitable tissue would make possible new avenues of basic and applied research involving blocking of activity or modulation of excitability in electrically active tissue.

Despite numerous investigations, a comprehensive understanding of the nature of current-induced neural damage remains elusive [8], with three persisting hypotheses: toxic environmental changes resulting from cellular “mass-action” [9,10], cytotoxicity resulting

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from electrochemical byproducts [11,12] and electroporation [13]. Waveform and electrode type likely dictate whether one or more of these mechanisms contribute to neural damage. In this study, we tested the hypothesis that toxic electrochemical products are responsible for damage resulting from DC delivery to nerve tissue, and demonstrate an electrode design which prevents this damage from occurring.

Methods

We evaluated the effect of prolonged DC delivery on acute nerve health in a rat sciatic nerve preparation using a left/right leg pair-controlled study. DC was delivered using one of either 1) a traditional platinum nerve cuff electrode or 2) an electrode in which the metal electrode and the nerve cuff interface were physically separated with a column of electrolyte, which we refer to as the “separated interface nerve electrode” (SINE). The SINE was used to keep any toxic electrochemical products (such as concentrated hydroxide ions or reactive oxygen species) from reaching the nerve [13,14]. Experiments were performed in five adult Sprague-Dawley rats under approval from our institutional animal care and use committee.

Surgical Preparation

The experiments were performed in a rat sciatic nerve and gastrocnemius-soleus muscle preparation which has been used in other nerve block studies in the rat [15–19]. The animals were anesthetized with intraperitoneal injections of Nembutal (sodium pentobarbital). The left hind leg was shaved and an incision was made along the posterior aspect of the hind leg and thigh. Approximately 20 mm of the sciatic nerve was exposed proximally from its branch point with the common peroneal nerve. The gastrocnemius-soleus muscle complex was dissected, and the calcaneal (Achilles) tendon was severed from its distal attachment at the heel. The ipsilateral tibia was stabilized to the experimental rig via a clamp, and the calcaneal tendon was tethered to a force transducer with 1–2 N of passive tension. Figure 1 shows a diagram of the experimental setup.

Experimental Design

The effect of DC delivery on acute nerve health was tested using two types of electrodes in a left/right leg pair-controlled rat sciatic nerve preparation. In the left leg of each animal, DC was delivered using a traditional platinum nerve cuff electrode. In the right leg of each animal, DC was delivered using an electrode in which the metal electrode and the nerve cuff interface were physically separated with a column of electrolyte (SINE) [13,14].

For each experiment, three electrodes were placed on the sciatic nerve (Fig. 1). The proximal and distal electrodes were used for delivery of low frequency (1 Hz – 3 Hz) test stimuli using a Grass S88 stimulator (Grass Technologies, West Warwick, RI, USA) with a current-controlled output stage. Test stimuli were monophasic cathodic pulses with supramaximal amplitude for motor fibers (typically 300 – 700 μ A) with a pulse width of 50 μ sec. The central electrode (either a traditional platinum cuff or a SINE) was used to deliver DC via a current-controlled Keithley 6221 waveform generator (Keithley Instruments, Cleveland, OH, USA). The DC return was a silver-silver chloride button electrode placed subcutaneously on the dorsum of the animal.

The proximal and distal test electrodes were bipolar silicone rubber nerve cuffs with a J-shaped cross-section and rectangular platinum contacts for current delivery [20]. Each electrode had a 2.0 mm edge-to-edge contact spacing and 1.0 mm of silicone between the outer edge of each contact and the edge of the cuff. Each rectangular contact had dimensions of 3.0 mm by 1.0 mm (the 1 mm dimension was along the length of the nerve). The platinum DC electrode was of similar construction, but with only 1 platinum contact for monopolar

delivery. This exact type of electrode has been used in several other studies in a rat sciatic nerve preparation [15–18,20].

The electrode-electrolyte interface of the SINE was a 2.5 cm long stranded stainless steel wire located in a 25 cc saline-filled syringe (Fig. 1). The syringe was connected to a polymer nerve cuff via a 15 cm silicone tube (~1.5 mm inner diameter). The nerve cuff was ~8 mm in length with an inner diameter of approximately 1.5 mm. The neural interface of the SINE was a ~1.0 mm² window in the center of the nerve cuff. The syringe and barrel were filled with 0.9% isotonic saline to provide a conductive pathway from the metal conductor to the nerve. The concept of utilizing a syringe for this electrode was to maintain a column of saline between the electrode and nerve by depressing the plunger as needed. In practice, we found that the saline did not rapidly flow out of the syringe or tubing, and it was rarely necessary to use the plunger. The SINE and platinum cuff electrodes exhibited a DC impedance of ~25 k Ω , and ~1.5 k Ω , respectively. The impedance was calculated as the DC electrode voltage divided by a 1.5 mA cathodic electrode test current as measured using a series 1 k Ω resistor. Impedance was measured using a silver-silver chloride return electrode. Compliance voltages of ~35V and ~2.5V were typical for the SINE and platinum electrodes, respectively.

Acute nerve health was tested by comparing the muscle twitch force generated by the proximal stimulation electrode to that generated by the distal stimulation electrode. This allowed for a direct assessment of the ability of the nerve region directly under the DC electrode to conduct neural impulses. For each experiment, cathodic DC pulses lasting 2–30 s were repeatedly delivered to the nerve via the center electrode at an amplitude equal to the DC block threshold [2], which was 1.4 ± 0.21 mA (mean $\pm$ stdev.) for the Pt electrode and 1.4 ± 0.30 mA for the SINE. Proximal and distal test stimuli were delivered during the brief periods between DC deliveries (5 – 8 sec in length). When enough DC was delivered to induce a prolonged suppression of conduction of the proximally elicited test stimuli, DC delivery was halted and 0.5 Hz proximal test stimuli were delivered to the nerve to monitor recovery of nerve conduction. These 0.5 Hz stimuli were delivered until complete nerve conduction was restored. Distal test stimuli were delivered periodically (~5–10 pulses/minute) to ensure proper normalization of proximally elicited muscle force.

When using the SINE, the nerve exhibited complete recovery after only seconds to minutes after cessation of the DC delivery. Once nerve conduction was fully restored in these trials, DC was again delivered until prolonged suppression of conduction occurred using the protocol described above. For four of the five animals, repeated DC delivery was performed at least six times using the SINE. In one animal, repeated DC delivery was performed five times. After the final DC delivery using the SINE, a 30 minute wait period was implemented. After the 30 minute wait, DC was delivered once again until prolonged suppression was induced and recovery was subsequently monitored.

Data Analysis

The time required to induce prolonged suppression (Fig. 2b) was calculated as the total cumulative DC delivery time required to produce prolonged suppression of nerve conduction. The recovery time (Fig. 2c) was calculated as the time required for the proximally elicited muscle force to recover from 10% of its maximal value to 90% of its maximal value.

Results

DC delivery with the platinum electrode resulted in rapidly irreversible nerve damage as evidenced by a complete suppression of proximally elicited muscle force after an average of 41.2 cumulative seconds of DC delivery, with partial suppression occurring after an average of 16.0 sec (time is cumulative over multiple deliveries -- Fig. 2a). Distally elicited muscle force was not affected by DC delivery. The status of the nerve was evaluated 2–4 hours after cessation of DC delivery and showed no recovery in two animals and minimal recovery in three animals (Fig. 2a). These results are consistent with previous studies describing DC-induced nerve damage [5–7].

DC delivery through the SINE produced very different results. Complete suppression of proximally elicited muscle force occurred after an average of 270 sec of DC delivery, approximately six times longer than DC delivery through the platinum electrode. Furthermore, nerve conduction was completely restored within seconds to minutes after halting DC delivery in each animal. Subsequent cycling of DC delivery through the SINE resulted in a similar suppression and complete restoration of nerve conduction (Fig. 2a). Each of the five animals tested exhibited very similar behavior, with temporary suppression and prompt and complete restoration of conduction with repeated DC delivery using the SINE. A total cumulative DC delivery of up to 880 seconds was tested in one animal with complete restoration of conduction. There was no obvious change in nerve appearance upon visual inspection after each experiment with the SINE or platinum electrodes, however, careful examination was not performed.

Repeated DC delivery resulted in an asymptotic decrease in the duration of DC required to induce prolonged suppression (Fig. 2b), and an asymptotic increase in the time required for conduction to be restored (Fig. 2c). When DC delivery was halted for a 30 minute wait period (in which there was no current delivered to the nerve), the time to suppression and subsequent restoration of nerve conduction rebounded toward initial values in every animal (Fig. 2, b and c).

Discussion

Within our one hour testing session, the SINE did not show any evidence of producing permanent damage to the nerve, in contrast to the traditional platinum nerve cuff electrode. These results provide compelling evidence that toxic electrochemical reaction products at the site of the electrode, and not mass action or electroporation, are responsible for DC-induced nerve damage. The majority of charge delivery was likely provided via electrolysis of water, given that the charge densities delivered using the Pt electrodes were approximately three orders of magnitude larger than that which can be safely delivered using the pseudo-capacitive platinum-hydride mechanism alone [8]. The electrolysis of water results in a local pH change and reduction of oxygen into reactive oxygen species that may explain the stimulation-induced toxicity [8].

The possible use of a SINE as a method for safely delivering DC to excitable tissue could be valuable as a laboratory research tool or potentially for clinical treatment of diseases which involve pathological neural or cardiac activity, such as pain, epilepsy, movement disorders, autonomic hyperactivity, pathological cardiac output, etc. A recent study has demonstrated the potential usefulness of combining high frequency alternating currents and ramped DC in producing prolonged, activity-free neural conduction blockade [21]. A SINE electrode could enable this technique to be used safely. Furthermore, a SINE architecture may also have application in expanding the usefulness of clinical stimulation involving very large charge

densities which currently result in tissue damage from toxic electrochemical products (e.g. cardiac defibrillation [22]).

This study provides some insight into the nature of the reversible prolonged suppression of muscle force which occurred when DC was delivered using the SINE. When DC delivery was halted for a 30 minute wait period, the time to suppression and subsequent restoration of nerve conduction rebounded toward initial values in every animal. These findings suggest that the prolonged suppression of conduction is likely the result of a fully reversible process (e.g. depolarization block induced by ion accumulation [23]).

The SINE architecture implemented in this study is sufficient for acute studies, however it is not suitable for chronic laboratory or implantable applications. A practical DC delivery system would likely involve a large surface area electrode interface utilizing a Faradaic or non-Faradaic charge transduction material with a high charge-storage capacity (CSC). Carbon-based materials currently used for the commercial production of electrochemical double layer capacitors or fuel cells may be appropriate candidate materials for permitting a large degree of safe DC charge transfer in a SINE configuration. Large volumetric surface area density could be achieved using three dimensional metal geometries within a tubed lead. Furthermore, an advanced electrolyte solution could potentially be used to buffer pH changes or inhibit the activity of reactive oxygen species. A low amplitude recharge phase could be used to ensure electrochemical reversal when the blocking current is not being delivered.

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Figure 1.

Experimental setup. Three electrodes were placed on the sciatic nerve: a proximal stimulation electrode, a DC electrode and a distal stimulation electrode. DC was delivered using a traditional platinum cuff-style electrode in one leg, and using a SINE in the other. Acute nerve health was monitored by assessing the ability of the nerve to conduct impulses through the region of the DC electrode (comparing proximally to distally elicited gastrocnemius muscle force).

Figure 2.

Experimental results showing that a SINE allows for safe delivery of DC to nerve. a) Typical results comparing DC delivery using a traditional platinum cuff electrode and a SINE. Abscissa is experiment time, and ordinate is proximally elicited muscle force normalized to distally elicited muscle force. Long-term (2–4 hour) recovery for the platinum electrode experiments is overlaid on the plot. (b-c) Data suggesting that DC-induced suppression using the SINE is a reversible phenomenon. b) The amount of DC required to induce prolonged suppression decreases asymptotically with cumulative DC, and rebounds after a 30 minute rest period. c) The time for recovery of conduction after DC-induced prolonged suppression increases asymptotically with cumulative DC delivery and rebounds after a 30 minute rest period.