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An implantable triple-function device for local drug delivery, cerebrospinal fluid removal and EEG recording in the cranial subdural/subarachnoid space of primates

Nandor Ludvig[a,*], Geza Medveczky[a], Richard Rizzolo[b], Hai M. Tang[a], Shirn L. Baptiste[a], Werner K. Doyle[a], Orrin Devinsky[a], Chad Carlson[a], Jacqueline A. French[a], John G. Kral[c], Jean Charchaflieh[d], Ruben I. Kuzniecky[a]

[a] NYU Comprehensive Epilepsy Center, New York University School of Medicine/NYU Langone Medical Center, 223 East 34th Street, New York, NY 10016, United States
[b] DocXS Biomedical Products, Ukiah, CA 95482, United States
[c] Department of Surgery, SUNY Downstate Medical Center, Brooklyn, NY 11203, United States
[d] Department of Anesthesiology, SUNY Downstate Medical Center, Brooklyn, NY 11203, United States

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ABSTRACT

Transmeningeal pharmacotherapy for cerebral cortical disorders requires drug delivery through the subdural/subarachnoid space, ideally with a feedback controlled mechanism. We have developed a device suitable for this function. The first novel component of the apparatus is a silicone rubber strip equipped with (a) fluid-exchange ports for both drug delivery and local cerebrospinal fluid (CSF) removal, and (b) EEG recording electrode contacts. This strip can be positioned between the dura and pia maters. The second novel component is an implantable dual minipump that directs fluid movement to and from the silicone strip and is accessible for refilling and emptying the drug and CSF reservoirs, respectively. This minipump is regulated by a battery-powered microcontroller integrating a bi-directional radiofrequency (RF) communication module. The entire apparatus was implanted in 5 macaque monkeys, with the subdural strip positioned over the frontal cortex and the minipump assembly secured to the cranium under a protective cap. The system was successfully tested for up to 8 months for (1) transmeningeal drug delivery using acetylcholine (ACh) and muscimol as test compounds, (2) RF-transmission of neocortical EEG data to assess the efficacy of drug delivery, and (3) local CSF removal for subsequent diagnostic analyses. The device can be used for (a) monitoring neocortical electrophysiology and neurochemistry in freely behaving nonhuman primates for more than 6 months, (b) determining the neurobiological impact of subdural/subarachnoid drug delivery interfaces, (c) obtaining novel neuropharmacological data on the effects of central nervous system (CNS) drugs, and (d) performing translational studies to develop subdural pharmacotherapy devices.

1. Introduction

Cerebral cortical disorders, untreatable with systemic pharmacology and surgical resection, might be treated with a device that can be chronically implanted in the subdural/subarachnoid space to perform therapeutic drug delivery through the arachnoid and pia maters into the underlying, diseased neocortex. This "transmeningeal pharmacotherapy" has been proposed for controlling focal neocortical seizures (Ludvig et al., 2006, 2009) and maximizing post-stroke recovery (Ludvig, 2010). Drugs delivered through the subdural/subarachnoid space have been shown to diffuse into the neocortical tissue and this diffusion can be controlled (Cornblath and Ferguson, 1976; Ludvig et al., 2008). However, a device chronically implanted in the subdural/subarachnoid space induces, like all other intracranial devices (e.g., ventricular shunts), an inflammatory host reaction by the surrounding tissue (Bruni and Del Bigio, 1986; Del Bigio, 1998). This can clog the drug delivery apparatus and hinder transmeningeal drug diffusion. Therefore, effective transmeningeal pharmacotherapy requires a device that can perform local drug delivery in a way that minimizes or eliminates the unwanted impact of inflammatory tissue reaction (e.g., via periodic removal of the local CSF loaded with inflammatory cells and molecules). Further, electrophysiological feedback, such as EEG recording, from the drug-exposed cerebral cortical area is also necessary to optimize the drug delivery parameters (e.g. concentration, delivery frequency, etc.). Thus, instead of using an apparatus like

* Corresponding author. Tel.: +1 718 270 1796; fax: +1 718 270 3103.
E-mail address: nandor.ludvig@nyumc.org (N. Ludvig).

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the intrathecal baclofen pump (Hsieh and Penn, 2006; Dykstra et al., 2007), subdural/subarachnoid pharmacotherapy must utilize a more complex device to execute the triple function of local drug delivery, cerebrospinal fluid removal and EEG recording.

In our previous publications (Ludvig and Kovacs, 2002; Ludvig et al., 2005, 2006, 2009, 2010a), we have described some technical aspects of such a complex device. However, the hardware of the entire subdural/subarachnoid apparatus, its surgical implantation and mode of operation in the chronically implanted animals have not been published. The aim of the present report is to provide these details. The animal tests were performed in freely behaving monkeys, as rodents are not ideal experimental subjects for implantation with a subdural/subarachnoid device to assess its clinical viability. Since the present device can yield information on the neocortical effects of transmeningeally administered drugs in monkeys during various behaviors and for many months its use can also provide new insight into the function of the primate neocortex.

2. Materials and methods

2.1. Animals

Five male, adult bonnet macaques (*Macaca radiata*) weighing 4.4–6.3 kg were used. The animals were obtained from the macaque colony bred and kept at SUNY Downstate Medical Center. All experimental procedures described in this paper were carried out in accordance with the National Institutes of Health Guide for the Care and Use of laboratory Animals (NIH Publications No. 80-23) revised 1996 and were approved by the Institutional Animal Care and Use Committees of NYU School of Medicine/Langone Medical Center and SUNY Downstate Medical Center. The device became clogged in the first monkey, leading us to recognize the importance of periodically washing out the accumulated host reaction cells and proteins. This procedure was implemented in the remaining 4 animals, eliminating the problem of clogging in all of them. Thus, the device worked flawlessly in 4 monkeys.

2.2. Design of the subdural/subarachnoid strip

The strip (US Patent Application No. 20100179518; US Patent Application Serial No. 12868890) comprises two components. One component is a custom-made subdural EEG recording strip from Ad-Tech Medical Instrument Corp. (Racine, WI). Specifications of this strip are: stainless steel electrode contacts embedded in medical grade silicone rubber; 2 mm contact diameter; 5 mm center-to-center contact spacing; 0.7 mm thickness (Fig. 1A). The other component is a proprietary, 21 mm × 14 mm medical grade silicone rubber strip integrating two fluid-exchange ports from DocXS Biomedical Products (Ukiah, CA). Specifications of this component are: 0.5 mm thickness; 50 durometer; 4.75 mm fluid-port ID; 0.3 mm thick supporting silicone layer. Two tubes open into each port. In our experiments one tube delivers saline or drug and the other withdraws local CSF. The inner and outer diameter of each of these tubes is 0.3 and 0.6 mm, respectively. The wires of the electrode-strip component are connected to a Mill-Max connector (Mouser Electronics, Mansfield, TX). One pin of this connector has an insulated wire to be connected to the reference electrode during surgery (see below). Thus, when prepared for implantation, the subdural strip (Fig. 1A) is already equipped with the Mill-Max connector. Table 1 summarizes the functions of the subdural strip.

2.3. Design of the control unit

Saline or drug delivery, CSF withdrawal and EEG recording via the subdural/subarachnoid strip are regulated by a control unit comprising a dual minipump (Fig. 1B) and a microcontroller, with

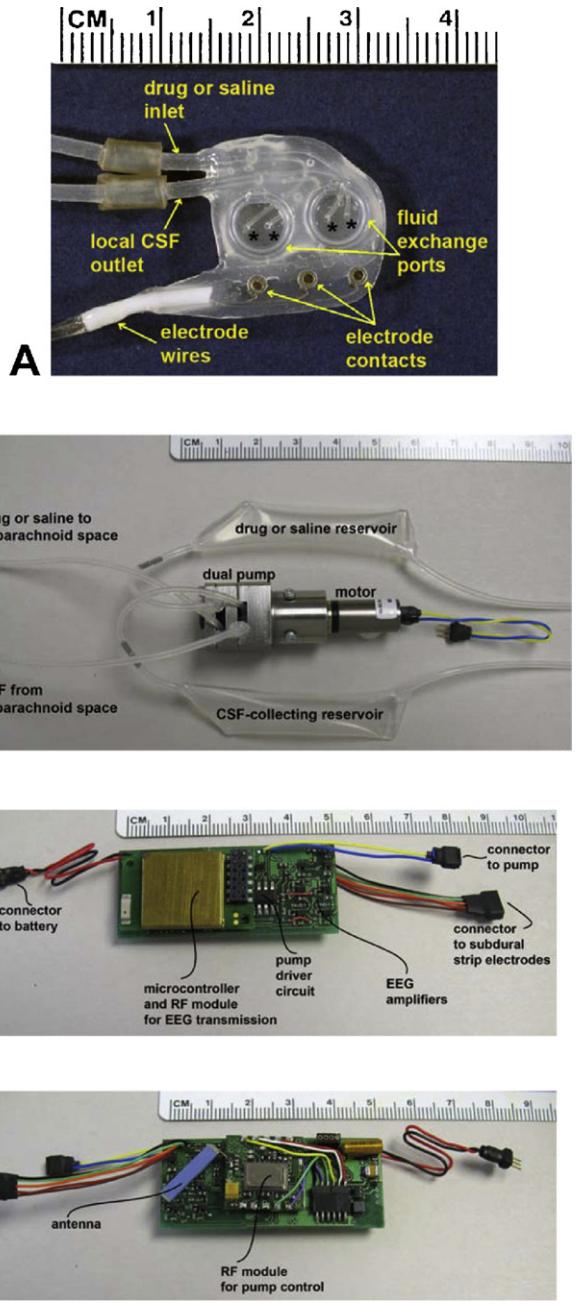

Fig. 1. Photographs of the key components of the implanted device. (A) The subdural/subarachnoid strip equipped with fluid exchange ports and EEG electrodes. (B) The dual minipump suitable for both saline or drug delivery and local CSF removal via the subdural/subarachnoid strip. (C and D) The two sides of the microcontroller board integrating EEG amplifiers, a microprocessor, and RF module, a minipump driver circuit.

the microcontroller integrated with a minipump driver circuit, EEG amplifiers and an RF communication module (Fig. 1C and D; Table 1). This unit is not MRI compatible.

The dual minipump is a 52 mm × 15 mm × 15 mm device weighing 25 g. It includes two independent peristaltic pumps driven by a single DC motor with a gear-head. A proprietary clutching mechanism allows the activation of either of these pumps. Each pump is connected to a 2.5 ml silicone reservoir (Fig. 1B), where one reservoir is filled with either saline or a drug solution for delivery, whereas the other one serves as a CSF collection reservoir. Since this was a methodological study devoted to troubleshooting, we checked the pumps and reservoirs biweekly. This procedure,