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Research report

Spatial memory in nonhuman primates implanted with the subdural pharmacotherapy device

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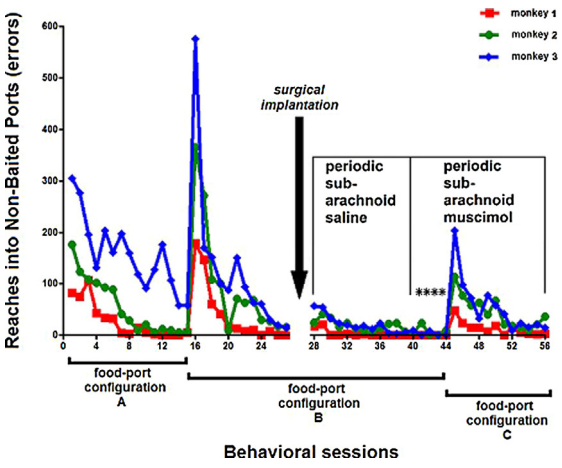
HIGHLIGHTS

- Spatial memory performance of macaque monkeys was tested over 6 months.
- Tests were done before and after subdural pharmacotherapy device placement.
- The implantation site was over the right parietal/frontal cortex.
- The device periodically delivered saline and subsequently 1.0 mM muscimol.
- Neither implantation nor saline or muscimol delivery affected spatial memory.

GRAPHICAL ABSTRACT



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ABSTRACT

This study investigated the possible influence of the Subdural Pharmacotherapy Device (SPD) on spatial memory in 3 adult, male bonnet macaques (*Macaca radiata*). The device was implanted in and above the subdural/subarachnoid space and cranium overlaying the right parietal/frontal cortex: a circuitry involved in spatial memory processing. A large test chamber, equipped with four baited and four non-baited food-ports at different locations, was used: reaches into empty food ports were counted as spatial memory errors. In this study of within-subject design, before SPD implantation (control) the animals made mean 373.3 ± 114.9 (mean ± SEM) errors in the first spatial memory test session. This value dropped to 47.7 ± 18.4 by the 8th session. After SPD implantation and alternating cycles of transmeningeal saline delivery and local cerebrospinal fluid (CSF) drainage in the implanted cortex the spatial memory error count, with the same port locations, was 33.0 ± 12.2 during the first spatial memory test session, further decreasing to 5.7 ± 3.5 by the 8th post-implantation session ($P < 0.001$ for trend). Replacing transmeningeal saline delivery with similar delivery of the $GABA_A$ receptor agonist muscimol (1.0 mM) by

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the SPD did not affect the animals' spatial memory performance, which in fact included at least one completely error-free session per animal over time. The study showed that complication-free implantation and use of the SPD over the parietal and frontal cortices for months leave spatial memory processes intact in nonhuman primates.

1. Introduction

We have developed a clinically viable medical device, the SPD, for the treatment of focal neocortical epilepsies resistant to systemic antiepileptic drugs and unsuitable for neurosurgical resection [17]. The device consists of two interconnected units. One is a subdurally implanted silicone rubber strip integrating fluid-ports for both transmeningeal drug delivery into the cortex and local CSF drainage through the subarachnoid space and pia mater. The silicone strip also contains EEG electrode-contacts to provide feedback on SPD treatment. The other unit is the control system comprising: (a) a minipump for intracortical drug delivery and local cerebrospinal fluid (CSF) drainage, (b) a microcontroller, (c) a module for wireless communication, and (d) a battery [16]. Although this control unit was designed to ultimately be insertable in the cranium [10], in the present study it served to close the craniotomy and was secured to the skull externally for easy access.

In general, the advantages of SPD-treatment are: (1) It is site-specific, delivering drugs exclusively into the symptom-generating cortical areas. This allows increasing the drug concentration to effective levels selectively in the site of pathology while relieving other tissues from unwanted drug exposure. (2) It provides transmeningeal drug delivery, bypassing the blood-brain barrier (BBB) without tissue-penetrating cannulas or catheters. This makes it possible to treat dysfunctional, damaged or degenerating cortical areas with large and/or lipophobic molecules otherwise not crossing the BBB, while neural tissue is not subjected to penetration-related damage. (3) It alternates transmeningeal drug delivery with the drainage of harmful/neurotoxic endogenous molecules from the extracellular space of the treated cortex. This "pharmacodialysis" procedure [10] facilitates clearance in the local extracellular milieu, optimizing the effects of the SPD-delivered drugs.

The possible interference of the SPD or other intracranial drug delivery devices with memory formation and retrieval is unknown. Yet, the clinical viability of localized drug delivery for brain disorders hinges on the safety of this technique: interference with memory functions would certainly exclude its clinical application. The SPD was shown to leave overall behavior and motor functions intact in nonhuman primates [14,16,17]. Based on these previous studies we hypothesized that the neocortical SPD used for several months does not affect spatial memory performance. The present study tested this hypothesis by adapting to macaque monkeys the spatial memory monitoring apparatus we originally developed for squirrel monkeys [13]. This apparatus is comparable to systems developed by others to examine spatial cognition in rhesus macaques [7].

The right frontal/prefrontal and parietal cortices are intimately involved in spatial cognition [4,19–21,24]. As a consequence, any detrimental effects of SPD-like drug delivery/drainage implants over these areas would be reflected in spatial memory impairment. The monkeys examined in this study were implanted with SPD over these brain regions.

Since we have accumulated a large body of data on the intracortical diffusion pattern, local electrophysiological effects and general safety of muscimol administration via transmeningeal delivery into the rat and monkey neocortex [14–17], we decided to use muscimol, a $GABA_A$ receptor agonist, as the test drug administered by the SPD. The concentration of the muscimol solution employed in this study was 1.0 mM, which is more than 40× lower than the concentration used to inhibit motor cortical functions by localized muscimol microinjection [2,25], with our dose about 500× less than the lowest psychotropic dose in humans [8,23]. At the same time, 1.0 mM muscimol delivered periodically into the frontal cortex over long periods via subarachnoid pharmacodialysis implants can achieve therapeutic (e.g., antiepileptic) effects [14,17], justifying the selection of this concentration for the present study.

2. Materials and methods

2.1. Animals

The subjects were three male, adult bonnet macaques (*Macaca radiata*) aged 59, 60 and 65 months with weights at the beginning and the end of the study of 4.4 and 5.0 kg for monkey 1; 5.9 and 6.0 kg for monkey 2, and 6.3 and 6.1 kg for monkey 3. To promote interactions between the singly-housed monkeys their 123 cm H × 91 cm W × 82 cm L USDA-compliant cages were placed close to each other. Monkeys 1 and 2 were housed in the same room, whereas monkey 3 was housed in an adjacent room, facing the cage of another (non-implanted) monkey. During weekdays, when the cognitive studies were performed, the regular diet of the animals consisted of 4 LabDiet 5037 biscuits, 20 g each, available for the monkeys only after the experimental sessions ended after 5:00 PM. During weekends, the animals had access to their regular diet ad libitum. Water was available for monkeys at all times, except during the cognitive tests.

All experimental procedures adhered to the standards detailed in the Guide for the Care and Use of Laboratory Animals Institute for Laboratory Animal Research, National Research Council, Washington, DC. (National Academy Press, 1996). The described protocol was approved by the Institutional Animal Care and Use Committees of NYU Langone Medical Center/School of Medicine and SUNY Downstate Medical Center.

2.2. Implant hardware and software

The hardware of the device comprises a subdural strip and a control unit, as described in detail [16]. Briefly, the former is a combination of a custom-made subdural EEG recording strip (Ad-Tech Medical Instrument Corp., Racine, WI) and a fluid-port-integrating, 21 mm × 14 mm medical grade silicone rubber strip (DocXS Biomedical Products, Ukiah, CA) with a combined thickness of max. 1.0 mm. The control unit comprises a custom-made dual minipump and a controller board for a C851F930 microprocessor (Silicon Laboratories, Austin, TX), a minipump driver circuit (Zetex, Chadderton, UK), OPA333 operational amplifiers (Texas Instruments, Dallas, TX), and a custom-made RF communication module. The dual minipump is 52 mm × 15 mm × 15 mm, weight 25 g, and comprises a delivery and a drain pump, each connected to a 2.5 mL silicone reservoir, one filled with either saline or muscimol (Sigma–Aldrich; St. Louis, MO) for delivery, the other for drainage of CSF. We used a 3.7 V/1400 mAh Li-Ion battery